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RECENT ADVANCES IN THE STUDY OF CARCINOGENESIS*

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In the whole of medical and biological investigation, no field has shown greater activity over the past quarter of a century than that of cancer research. Indeed, such activity is constantly expanding, and will doubtless continue to do so until it results in a substantial contribution to the treatment and prevention of the disease in man. The practical problem is in itself of growing importance, and is without question, and very properly, the mainspring of the vast research effort now under way. Apart from the humanitarian aspect, however, it is well to recognize that the cancer problem also presents a more purely intellectual challenge, and it will surely rank as one of man's greatest achievements when he is able to control abnormal multiplication of the cells of which his very frame itself is made. The growth of cancer research also reflects the growth of modern biology as a whole, deriving much from it, and contributing much in return. Those it attracts have not merely great responsibilities but great opportunities as well, and may indeed be building perhaps better than they know, not only towards the understanding of a disease, but in the wider advancement of biological knowledge.

Approaches to the cancer problem are without number, yet a major part of the more fundamental approach is very naturally concerned with etiology, partly for its own sake as the central aspect, and partly in the confidence that a sufficiently profound knowledge of the process of causation will indicate methods by which, even in its latest stages, it may be modified or controlled. In the past, the subject has perhaps suffered from the division of opinion into two schools of thought, one ascribing the disease to the operation of what may loosely be described as biological and chemical factors, and the other to the action of a species of ubiquitous virus. In a sense, both schools are at once right and wrong, both having based interpretation upon facts, and both having minimized or disregarded other facts equally cogent. At the present time, the balance is probably in favour of an intrinsic cellular alteration as the primary cause, rather than the action of some extraneous infective agent. Yet no fact invalidates another, and hence it follows that no explanation can be complete, or finally acceptable, which fails to take account of all the facts available, of whatever kind. Fortunately, profitless discussion is largely giving way to extended investigation, both of the detailed process of chemical carcinogenesis on the one hand, and of the chemical and biological properties of the so-called tumour viruses (for example, the Rous chicken tumour virus, the virus-like agent associated with the expression of mammary cancer in mice, and the Shope virus causing rabbit papillomatosis) on the other.

* A paper presented in a symposium on the Etiology and Diagnosis of Carcinoma held in plenary session at the South African Medical Congress, Pretoria, October 1955.

CARCINOGENETIC SUBSTANCES

Progress in cancer research was greatly stimulated by the first experimental reproduction of the disease, by the Japanese in 1915, through the application of coal tar to the skin in rabbits. By stages, this eventually led to the recognition of at any rate one of the active agents, by my predecessor Kennaway and his school (namely, of the aromatic hydrocarbon 3 : 4-benzpyrene) and to the synthesis of a whole series of chemical carcinogens based on the benzanthracene, pyrene, chrysene and phenanthrene hydrocarbons. The fact that many naturally-occuring substances, including the bile acids and sex hormones, possess somewhat similar condensed polycyclic systems suggested that one of the most potent carcinogenic substances which this programme had disclosed, namely 20-methylcholanthrene, might in fact be produced in the tissues, through a perturbation of steroid metabolism, and so account for the natural causation of the disease. There is as yet no proof that changes of this kind take place *in vivo*, and chemists are still divided, and the majority doubtful, as to their

likelihood. In addition, recognition of carcinogenicity in many different chemical types proved beyond doubt that the malignant change can be precipitated by a wide range of agents, and reduced the likelihood that any one group might be of specific importance in natural causation.

Carcinogenetic Hydrocarbons

The discovery of carcinogenicity in the polycyclic hydrocarbons eventually led to a fascinating system of relationship between biological action and chemical constitution. Yet it is a remarkable fact, in spite of the wealth of our accumulated knowledge, that we still have no precise understanding either of the intracellular site at which these agents operate, or of the mechanism by which they evoke their characteristic biological response. In spite of this, in more recent years, the French school of theoretical physics has made a major contribution towards the solution of the problem, according to which carcinogenicity is linked with various active centres of the carcinogenic molecule, and is dependent upon a certain minimum numerical value of a complex energetic index which, so to speak, summarizes the reactive properties of the individual molecule as a whole.

Such studies are, of course, not merely of interest in their own right, but are directly relevant to the metabolic conversions which the carcinogenic hydrocarbons undergo *in vivo*, and to the nature of the biological substrates with which they combine. Knowledge of the former has been advanced by the studies of Boyland and his associates, among others, while the nature of the cellular substrates has been partly elucidated by Heidelberger and others working in Madison. In the interaction of carcinogenic hydrocarbons with tissue constituents, of special interest are certain protein-bound complexes formed after the topical application (to the skin of mice) of radio-dibenzanthracene. This chemical binding is irreversible, occurs only *in vivo*, is not due to surface adsorption, and takes place between the carcinogen or its metabolite and the nucleoproteins, particulate proteins and soluble proteins, but not with nucleic acids; and it recalls the somewhat similar combination of azo-carcinogens with liver proteins in the induction of liver cancer—also described by the Madison school—which will be referred to later.

Our appreciation of carcinogenesis by the aromatic hydrocarbons has been greatly assisted by Berenblum's analysis of the process as occurring in two main stages—an initiating reaction which results in a sudden and permanent change in the potentiality of the normal cell, and secondly a promoting action which he has recently suggested may act by delaying maturation, and so allowing a sufficient number of undifferentiated daughter cells to accumulate until they reach a colony of critical size. In its essentials, carcinogenesis is almost certainly the outcome of a direct interference by the carcinogen with the hereditary equipment of the cell. At the same time, we must not overlook the influence which may be exerted upon it by a wide range of nutritional, hormonal and genetical factors in the cell's environment—that is, by the nutrition, endocrine status and constitution of the host itself.

Whilst in general terms the carcinogenic hydrocarbons exert their influence mainly at the site of immediate application, other classes of carcinogen do so at remote sites—a feature in part determined in such cases by factors of absorption, transport and metabolism. Of these, good examples are found in many azo-dyestuffs, and especially in derivatives of 4-dimethylaminoazobenzene—commonly known as 'butter yellow', from its former use as a food colouring matter and additive. Here, the compound produces little effect locally when injected subcutaneously or administered in the diet, but elects to induce tumours in a distant organ, namely, cholangiomas and hepatomas in the liver. Once again, much is known of the relationship between the chemical constitution of such compounds and their biological action.

But the most recent emphasis has been concentrated on their mode of action, with results of the highest interest. In particular, the Madison school have studied the combinations taking place *in vivo* between such carcinogens and tissue constituents, and have advanced the view—somewhat similar to that which is gradually being approached by the writer and his own school from altogether different evidence—that the induction of malignant change is attributable to the gradual deletion of key proteins or enzymes essential for the control of growth. This important conception is supported by still other and independent evidence, immunological and biochemical, which also suggests the reality of protein-elimination in the course of liver carcinogenesis. Thus, in a study of the serological organ-specificity of the liver, using a fluorescence method of antigen detection in the process of carcinogenesis with butter yellow, facts have been adduced by Weiler of Tubingen to indicate that this is accompanied by the gradual deletion of a liver antigen.

Again, numerous electrophoretic studies of the soluble proteins from the livers of rats fed with aminoazo dyes show first that the metabolic derivatives of these dyes are capable of binding specific liver proteins, and secondly that the soluble proteins of the supernatant tumour-fractions undergo a great decrease in the lower mobility-component as compared with normal. The nature and function of the affected protein-component have not as yet been more clearly defined. Obviously this is a task of the utmost importance, and in particular it is necessary to decide which enzymatic activities, if any, have been damaged or eliminated in the process.

As in carcinogenesis with the aromatic hydrocarbons, so too is liver-tumour induction by the aminoazo dyes markedly susceptible to nutritional and hormonal influences. Indeed, these tumours are the only examples the appearance of which can be completely or nearly completely prevented by simultaneous administration, with the carcinogen, of adequate levels of a known vitamin, namely riboflavin. Hypophysectomy also effectively inhibits the carcinogenic action of these substances, and there is evidence to suggest that a pituitary-adrenal relationship may indeed be a prerequisite in the process of tumour induction in the liver. The complex nature of such endocrine influences is shown by the fact that the inhibition of carcino-

genesis by hypophysectomy may in part be annulled by treatment with ACTH, although not with the growth hormone, thyrotrophin or the gonadotrophins. This possible role of ACTH in carcinogenesis is further substantiated by the discovery that hypophysectomized rats injected with the carcinogenic hydrocarbons benzpyrene or methylcholanthrene exhibit an increased tumour-incidence when simultaneously treated with ACTH.

Carcinogenetic Amines

Our knowledge of yet another class of chemical carcinogen, namely the aromatic amines, sprang from the observation of the occupational hazard in the dyestuffs industry produced by such agents as beta-naphthylamine and benzidine, and due to their predilection for the urinary tract and especially their liability to evoke cancer of the bladder. Later, however, it was extended to include other amines such as the insecticide 2-acetylaminofluorene, and various derivatives of 4-aminostilbene and of 4-aminodiphenyl, the experimental investigation of which, as in other cases, has done much to extend our understanding of the carcinogenic process and the nature of the cancer cell.

Tumours of the urinary bladder in workmen engaged in the manufacture or use of dyestuff intermediates in the chemical industry still represent a practical problem, of which the nature and extent have recently been studied in a comprehensive fashion by Case and his colleagues at the Chester Beatty Research Institute. Experimentally, use is being made by others of isotopically labelled beta-naphthylamine in order to follow the metabolic fate of this substance, and the same tracer techniques are being applied in the case of 2-acetylaminofluorene, which is capable of producing not only bladder cancer in various species, but also hepatomas and a range of tumours of many other organs, the nature and distribution of which are reminiscent of those induced by the aminostilbenes.

The most recently described carcinogenic amines are 4-aminodiphenyl and its derivatives, the parent compound being described as more effective in producing cancer of the bladder in the dog than either benzidine or 2-acetylaminofluorene, and at least as potent as beta-naphthylamine. From their chemical nature, the carcinogenic amines present special problems and opportunities in attempts to elicit their mechanism of action. It has been suggested by Clayson that these substances are carcinogenic because of their conversion to *ortho*-hydroxyamines, a conversion which is facilitated if the position *para* to the aromatic amino group is blocked to biological hydroxylation. However, much further investigation is required, and Elson in particular has pointed out that whilst it is certainly possible that *ortho*-aminophenols are potentially carcinogenic, other factors—for example excretion as ethereal sulphates rather than as glucuronides (in which form are excreted the carcinogens benzidine, 4-aminodiphenyl and 4-aminostilbene)—may greatly modify their action.

A recent contribution of much interest is the demonstration by Boyland and his co-workers that cancer of the bladder in man is commonly accompanied by abnormally high levels of urinary glucuronidase; whether this is of etiological significance or is merely a secondary result still remains to be determined. As for other examples already quoted, the carcinogenic action of the amines is markedly susceptible to environmental circumstances, and especially the dietary regime. In particular, high levels of protein intake can exert a protective influence against tumour induction by 2-acetylaminofluorene and the aminostilbenes. Endocrine factors may also play a part, as in inhibition of the hepatoma-inducing action of 2-amino- and 2-acetylaminofluorene as the result of hypophysectomy.

MECHANISM OF CARCINOGENESIS

Exploration of the kinds of molecule capable of carcinogenicity is by no means even yet complete, but nevertheless there has been a change of interest and emphasis in the past 10 years towards the study of the problems of the mechanism of action. It is remarkable that in none of the cases above mentioned, in spite of great effort, can we state the precise site of action in the cell. In the past 6 years, however, there have been obtained the first hints—and even now they remain no more—of the likely site of action of at least one class of chemical carcinogen, from the discovery of carcinogenic activity in a series of nitrogen mustards—a group of nitrogen analogues of mustard gas endowed with the faculty of reproducing, by chemical means, many of the biological effects previously regarded as characteristic of ionizing radiations. The discovery of carcinogenic activity in this new chemical class, in compounds of relatively high chemical reactivity, simple in structure and yet possessing chemical features highly suggestive as to their mechanism of action, has led to speedy progress and to a theory of action which has in turn stimulated many other developments. At an early stage, it became obvious that the tumours induced by the aromatic nitrogen-mustards showed an exceptional incidence of nuclear abnormalities, similar in character to those produced by the same compounds in the division of normal cells. The fact that in a few cases at least the abnormalities persisted for a time in the serial transplantation of such tumours, suggested that the malignant cells in these cases bore the imprint of the carcinogen which had induced their appearance, in the form of a self-propagating structural change.

Such changes inevitably recall the repeated observation of nuclear imbalance in tumours generally, and once more draw attention to the nucleus as a possible primary site of carcinogenic action. At the same time, such gross anomalies are almost certainly not causal, but merely associated events, and the essential alteration underlying malignancy is probably much more specific and elusive. The biological activity of these interesting compounds is associated exclusively with the presence in the molecule of at least two of their characteristic 'haloalkyl' side-chains, and this circumstance led to the hypothesis that they may act by combination with contiguous linear macromolecules in the substance of the chromosome itself, by a process of chemical 'cross-linkage' as a stage in the induction of the cytological abnormalities observed, and possibly of the carcinogenic process itself. This view is now known to be unduly simple, and other

alternative possibilities are equally likely. All, however, embrace the general conception of a direct combination between the carcinogen and genetic receptors. In spite of its only partial truth, this working hypothesis—like so many in the history of science—has abundantly justified itself by the powerful stimulus to which it has given rise. At once it suggested the biological examination of various polyfunctional chemical substances already used as cross-linking agents in the textile industry, with the result that various di-epoxides and ethyleneimines, and other agents such as the methylolamides specially studied by F. L. Rose at Manchester, were soon recognized as capable of producing, by a similar mechanism, the cytotoxic and other biological effects previously regarded as characteristic of the mustards. The hypothesis also stimulated the synthetic development of new types of bifunctional agent, and in this way both cytotoxic and carcinogenic properties were detected in members of a series of dimethane sulphonyloxyalkanes, one member of which (1 : 4-dimethanesulphonyloxybutane or 'Myleran') has a relative specificity for cells of the myeloid series, and has been used with some success in the treatment of chronic myelogenous leukaemia.

Biological Alkylation

Whatever the mechanism of action of carcinogens as a whole, there is little doubt of the importance which their combination with genetically determinant material or its precursors would have, if this is, as seems likely, an essential part of the action of those more recently discovered carcinogens at least which function through biological 'alkylation'. An older view regarded the primary step in chemical carcinogenesis as an inhibition of the normal growth mechanism, leading to the adaptive formation of a new cell variant, released from the inhibitory influence of the agent which provoked it. The newer interpretation suggests that the primary step may be the inhibition of certain fundamental processes of genetic synthesis, followed by the generation of a new self-duplicating fibre or template chemically, and hence genetically, modified. In other words the cell undergoes a permanent re-orientation of genetic characters, under the impress of the chemical modification of an initial self-duplicating unit.

Here may be mentioned a possibility which is fraught with much potential significance for the 'spontaneous' origin of cancer, especially in its relation to ageing, and which arises from the fact that the alterations in cellular proteins which it is suggested are brought about by the biological alkylating agents, whether by cross-linking or other means, are similar to, or identical with, those occurring in the ageing of proteins and of many natural and artificial polymers. In such cases (as in the biological situation) two processes are involved, namely aggregation on the one hand, and degradation on the other. So far as concerns the theory of ageing, the effects of cross-linking on proteins, and the changes which proteins undergo in the ageing organism, appear to be identical; for example, brittleness, loss of elasticity and reduced solubility.

Genetic Modification

What is the nature of the genetic modification which the alkylating carcinogens evoke? By the methods at present available this is impossible to decide in the tumour cell directly, but suggestive evidence is provided by the circumstance that many of these agents are not merely carcinogenic but act as biological mutagens more widely. The cytogenetic analysis of the action of the newer carcinogens on the chromosomes of the fruit fly *Drosophila* indicates that these induce a molecular 'disablement' of certain genes, the affected gene reproducing itself either partially or erroneously or not at all.

For some considerable time the general biological evidence has pointed, even if rather vaguely, to the probability that the cancer cell represents a somatic mutation by loss. The latest evidence that the alkylating carcinogens may interfere with the synthesis and reproduction of genetic material is in keeping with and, although not yet conclusive, supports the view that the essential change in the cancer cell may be a deficiency, genetic or enzymic in character; or in other words that the cancer cell is a special kind of nutritional variant.

In spite of the great developments over the past 20 years in our knowledge of the nutritional control of growth in bacteria and fungi, little comparative information is available concerning substances critical for the growth of animal cells. However, one possible example has now been encountered in the case of the naturally occurring pigment xanthopterin, and of several related pyrimidines, administration of which in many species induces an increase of kidney size due to direct stimulation of mitotic activity in the tubular epithelium. This situation is highly suggestive of a device by which the normal growth and compensatory hypertrophy of the kidnev may be regulated and controlled by its dependence upon an essential factor which the organ is unable to synthesize and which must be supplied from elsewhere. It is also tempting to speculate whether the co-existent enzyme for which xanthopterin is the substrate, namely xanthine oxidase, may not play a part in regulating the concentration of the pterin at any given time, and whether inhibition or removal of the enzyme might not allow substrate accumulation and the release of cell division, in this specific tissue, from its normal control. The mechanism suggested—the release of growth-promoting synthetic reactions or the accumulation of growth-promoting substrates by enzyme modification or loss—is by no means novel, and is supported by other evidence. It will not have escaped attention that the possible role of enzyme deletion in carcinogenesis would indicate a specific if elusive difference between normal and malignant cells, with implications concerning the means by which the process might be ultimately controlled, whether by enzyme substitution or substitution of the reaction products of the substrate. Meantime, certain correlations are at any rate being approached, as for example between the chemical structure and properties of given carcinogens, their apparent combination at certain chromosome regions, the cytological effects so induced, and the genetic consequences to the cell which thus ensue.

It is perhaps a measure of progress that while less than

40 years ago the laboratory mouse was selected for the experimental study of carcinogenesis, on account of its high susceptibility, short life span, and ease of maintenance, the search should now be for biological material with specially favourable cytology. The present approach is also much more of a physiological kind than previously, at least as much attention being given to the regulatory mechanisms by which the growth-potency of normal cells is controlled as to the effects of their absence in the nearly autonomous growth of malignancy; both aspects are vitally connected, and much is being learned of each from study of the other. The cancer cell, it is commonly said, has acquired the power of unlimited growth; 25 years ago, J. A. Murray, then Director of the Imperial Cancer Research Fund, pointed out that this could hardly be true, since the same power already resides in the cancer cell's normal precursor. Simple and straightforward as this comment appears, it is none the less penetrating, and it is only perhaps of recent years that we have begun to comprehend the truth behind it: that, in order to explain the growth properties of the cancer cell, it is necessary to understand the growth potential of the normal cell upon which they are based, and the mechanisms by which this is subject to physiological regulation and control. If we are still a long way from this true understanding, hints at least are beginning to appear.

Early in the history of cancer research, two main conclusions were very quickly reached from observation of the cancer cell's behaviour: first that the malignant cell and the embryonic cell are in many ways remarkably similar; and secondly that malignant transformation involves an essentially regressive change, a more or less pronounced simplification, or reversion to a less specialized function. Further progress had to await another two stages: first the experimental reproduction of the disease by physical and chemical means, and secondly the detailed biochemical study of the carcinogenic mechanism. As has been seen, this last phase of investigation has been greatly intensified over the past 10 years. Chemical carcinogenesis can be regarded as a very special case of the action of drugs on cells, and much work is accordingly being directed to the nature of the cellular substrates with which the carcinogens combine. Already there is evidence, independently and from several different sources, that the combination may lead, either directly or indirectly, to the elimination of certain key proteins essential in the normal regulation of growth—so liberating more primitive synthetic reactions upon which the process of cell division depends, and from the uncontrolled impetus of which it now proceeds more or less continuously. Here is evidence which points, in parallel with the biological dedifferentiation of the cancer cell which has been recognized for so long, to a chemical dedifferentiation involving some loss of the mechanisms normally controlling protein synthesis.

FUTURE OF CANCER RESEARCH

What are the aims and the trends of cancer research today? The paramount aims are first the understanding—in physiological, genetical, and chemical terms—of the process of cell division, and secondly its practical control. Thus far, the progress of the past 20 or 30 years appears to provide a complete denial of the dictum of Max Planck (in 1932) that scientific knowledge and scientific discovery have been achieved only by those who have gone in pursuit of them without any practical purpose whatever in view; certainly they have been achieved only by those who have adopted a sufficiently broad approach, but subject to this it would seem that a human purpose, far from being a bar, may on the contrary provide a stimulus and incentive of unequalled power. It is not given us to penetrate the future, but it may well be that the history of cancer research will resolve itself into three main phases; first the impartial exploration of every avenue of attack, secondly the definition and limitation of those few that are decisive in strategy, and thirdly—still beyond our ken—a phase of conscious development. More than half-way through the 20th century, and after 50 years of cancer research in its modern sense, it seems we are now at last approaching 'the end of the beginning'.

ASSOCIATION NEWS : VERENIGINGSNUUS

ANNUAL GENERAL MEETING QUEENSTOWN DIVISION

The Annual General Meeting of the Queenstown Division of the Medical Association of South Africa was held at the Frontier Hospital, Queenstown, on 17 November 1955 at 8.15 p.m.

Dr. M. I. Papilsky took the chair in the absence of the President, Dr. A. Voortman. Members expressed regret at Dr. Voortman's serious illness, wished him a speedy recovery, and directed that the good wishes of the meeting be conveyed to Dr. Voortman.

The financial statement showing a credit balance was adopted.

Correspondence: Letter re National Medical Aid Society. Dr. Schaffer gave information on this matter and a short discourse on medical aid societies and benefit societies.

The following officers were elected: *President*—Dr. M. I. Papilsky; *President-Elect*—Dr. G. Dall; *Honorary Secretary and Treasurer*—Dr. D. M. Holmes; *Elected Members of Executive Committee*—Drs. R. Schaffer, J. M. van Schalkwyk, A. Rosin, H. A. Luiz; *Representatives on Border Branch Council*—Drs. G. Dall, P. A. Goodwin, J. M. van Schalkwyk, R. Schaffer (member of Federal Council), M. I. Papilsky and D. M. Holmes (*ex officio*); *Nominees on the Queenstown Hospital Board*—Drs. J. M. van Schalkwyk and A. Voortman.

Dr. P. A. Goodwin submitted a clinical case as follows: Native female aged 25. First seen in gross cardiac failure with a large heart and a pulse rate of 200 a minute, regular. Pulse rate halved by eyeball pressure, but not affected by pressure or massage of the carotid sinus. Diagnosis of paroxysmal atrial tachycardia made on clinical grounds. Intravenous digitalization did not affect the pulse rate and quinidine was therefore given in dosage of 6 gr. 2-hourly. After the 4th dose tachycardia remitted and the pulse rate has remained steady at 80 per minute on maintenance quinidine. Examination revealed a grossly enlarged heart with rheumatic mitral stenosis and aortic regurgitation.

The meeting closed at 10 p.m. with a vote of thanks to the superintendent and matron of the hospital for refreshments kindly supplied during the year.

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EDITORIAL

ANTIBODIES

The immunity which is acquired after recovery from certain infectious diseases is often associated with the appearance in the blood stream of specialized globulins, usually gamma globulins. In experimental work a large variety of cells and protein molecules have been used (usually by injection into the body) to stimulate the formation of antibodies. By the use of these artificial antigens and with the purification of antibodies a better understanding of immunological reactions has been made possible.[1] The association of antibodies with serum globulin was known in 1910, but only in recent years has it become accepted that antibodies are globulin molecules. The difficulty in establishing their true nature has been due to the difficulty experienced in purifying and characterizing proteins. Some antibodies, for example diphtheria antitoxin, have been obtained in highly active form. The fractionation of plasma proteins enabled concentrated antibody fractions to be obtained. The development of the ultracentrifuge by Svedberg and the analytical electrophoretic apparatus by Tiselius made it possible to study the physical properties of antibodies.

Most antibodies appear to be indistinguishable from normal gamma-globulin, but there are some which are of higher molecular weight than the normal; in horses immunized with diphtheria toxin or tetanus toxin a new component appears on electrophoresis, which migrates between the beta and gamma globulins. Analyses that have so far been made have shown no significant differences in the amino-acid composition of antibodies and of corresponding normal serum proteins. At some point in their molecules antibodies must have peculiarities which give them their immunological properties. The reaction with antigen probably depends on particular arrangements at certain combining sites of the antibody molecule. The number of such combining sites is known as the valency of the antibody.

The forces involved in the combination of antigen and antibody are chemical, but other forces may be important. The ideas of modern structural chemistry suggest that van der Waal's forces, hydrogen bonds, and Coulomb forces, may all play a part in the combination of antigen and antibody.[1]

VAN DIE REDAKSIE

TEENSTOWWE

Die onvatbaarheid verwerf na herstel van sommige aansteeklike siektes word dikwels in verband gebring met die verskyning in die bloedsomloop van gespesialiseerde globuliene—gewoonlik gammaglobuliene. 'n Groot verskeidenheid selle en proteïenmolekules is al gedurende navorsing gebruik (gewoonlik deur inspuiting in die liggaam) om die vorming van teenliggaampies aan te spoor. Danksy die gebruik van hierdie kunsmatige antigene, en die suiwering van teenstowwe, het 'n beter begrip van weerstandsreaksies moontlik geword.[1] Reeds in 1910 was dit bekend dat daar 'n verband tussen teenstowwe en serum-globuliene bestaan, maar dit is eers in later jare algemeen aangeneem dat teenliggaampies inderdaad globulienmolekules is. Dit was juis so moeilik om hulle eintlike aard te bepaal weens die moeilikhede ondervind in die suiwering en karakterbepaling van proteïene. Sommige teenstowwe, soos byvoorbeeld die witseerkeel-antitoksien, is al in hoogs aktiewe vorm verkry. Die fraksioneer van plasmaprote ene het navorsers in staat gestel om gekonsentreerde teenstofdeeltjies te bekom. Deur die ontwikkeling van Svedberg se ultrauitswaai-apparaat en die analitiese elektroforesetoestel van Tiselius is dit tans moontlik om die fisiese eienskappe van teenstowwe te bestudeer.

Blykbaar is die meeste teenstowwe moeilik te onderskei van normale gammaglobulien, maar daar is 'n paar wat 'n hoër as normale molekulêre gewig besit. By perde wat met witseerkeel- of tetanustoksien gesout is, kom daar onder elektroforese 'n nuwe bestanddeel na vore wat tussen die beta- en gammaglobuliene omskakel. Dusver het ontledings geen betekenisvolle verskille tussen die aminosuur-samestellings van teenliggaampies en van ooreenkomstige normale serum-proteïene onthul nie. Iewers in hul molekules moet teenstowwe eienskappe besit waaraan hulle hul immuniteitskragte ontleen. Die reaksie met antigene berus waarskynlik op besondere rangskikkings by sekere setels van verbinding. Die aantal van sulke verbindingspunte staan bekend as die valensie van die teenliggaampie.

Die kragte wat by die verbinding van antigene met teenstowwe betrokke is, is chemies van aard, maar daar is ander kragte wat ook van belang mag wees. Die rigting van moderne denke in struktuurchemie suggereer dat die Van der Waal-kragte, waterstofbomme, en die kragte van Coulomb almal moontlik deel in die verbinding van antigeen en teenliggaampie.[1]

Die produseer van teenliggaampies gedurende aktiewe immunisasie word beheer deur 'n aantal faktore. Reaksie

The production of antibodies during active immunization is governed by a number of factors. The response to the antigenic stimulus occurs in two stages. In the 'primary response' the production of antibody may be trivial, but the important feature is the conditioning effect which makes the antibody-producing mechanism very responsive to subsequent administrations of the antigen. This conditioning effect may last for years. It takes some time to develop to a maximum. The practical importance of this is shown, for example, in the active immunization of children against diphtheria; among other factors the time-interval between the doses of toxoid is important in determining the production of antibodies.

The secondary response, in which the synthesis of antibody globulin occurs, would appear to be due to increased production of antibody rather than the release of stored antibody. There then follows a phase of decline, at first rapid but gradually flattening and remaining almost constant for a long time, usually at a titre greater than that originally present. The decline is due to metabolism of the serum protein, the rate of disappearance of the antibody being determined by a number of factors; at the same time there is continued production of antibody.

There would thus appear to be two distinct mechanisms for the production of antibodies; firstly, in the conditioning effect (the establishment of potential immunity), and secondly in the manufacture of antibody globulin. The synthesis of antibodies is a chemical process, but the way in which they are formed is still uncertain.[1] According to Pauling the molecule is formed as a polypeptide chain the ends of which fold in a manner complementary to the surface of an antigen in the vicinity; possibly the antigen guides the synthesis of further antibody molecules, which then remain attached to it or break away from it. According to other workers (Burnet and Fenner) the antigen modifies not the globulin molecules but a self-duplicating unit in the cell in which these molecules are synthesized.

1. Abraham, E. P. in H. Florey. ed. (1954): London: Lloyd Luke, Ltd.

op die antigeniese prikkel vind in twee fases plaas. In die primêre reaksie mag teenstofproduksie niksbeduidend gering wees, maar die belangrikste feit hier is die bereidende uitwerking wat die teenliggaampie uiters sensitief maak vir verdere toedienings van die antigeen. Hierdie bereidende uitwerking kan jare lank van krag wees. Dit neem tyd om tot op volle sterkte te kom. Die aktiewe immunisasie van kinders teen witseerkeel is 'n goeie voorbeeld van die praktiese belang van hierdie feit; onder andere is die verposing tussen dosisse toksoïed van belang in die bepaling van teenstofproduksie.

Waarskynlik word die sekondêre reaksie (wanneer die sintese van teenstofglobulien plaasvind) eerder veroorsaak deur vermeerderde produksie van teenliggaampies as deur die vrystelling van bewaarde teenliggaampies. Dan volg 'n fase van afname, eers snel maar later geleidelik stadiger, totdat dit eindelik vir 'n lang tyd feitlik konstant staan—gewoonlik op 'n titer meer as die hoeveelheid oorspronklik teenwoordig. Die afname word veroorsaak deur die metabolisme van die serum-prote ene, en die snelheid waarteen die teenstof verdwyn word deur verskillende faktore bepaal. Terselfdertyd gaan die liggaam voort met die vervaardiging van teenliggaampies.

Dit blyk dus dat daar twee afsonderlike meganismusse is vir die produksie van teenstowwe; eerstens is daar die bereidende uitwerking—wanneer potensiële immuniteit verleen word—en tweedens, die vervaardiging van teenstofglobulien. Die sintese van teenstof is 'n chemiese proses, maar hoe hul vervaardig word is nog 'n duistere saak.[1] Volgens Pauling word die molekule gevorm as 'n ketting van polipeptiede, en die ente van die ketting vou dan op 'n wyse wat aanpas by die oppervlakte van 'n nabye antigeen. Waarskynlik beïnvloed die antigeen die sintese van verdere teenstofmolekules wat òf daaraan geheg bly òf anders wegbreek. Volgens ander werkers (Burnet en Fenner) is dit nie die globulienmolekules wat deur die antigeen gewysig word nie, maar wel 'n selfverdubbelende eenheid in die sel waarin hierdie molekules hul oorsprong het.

1. Abraham, E.P. in H. Florey, red. (1954): Londen: Lloyd Luke, Ltd.

CANCER RESEARCH

The Pretoria Congress Committee chose wisely in making Cancer the keynote of this year's South African Medical Congress by selecting it as the subject for the plenary sessions. They also did well to invite certain distinguished British workers in the field of malignant disease to contribute to these symposia. Notwithstanding the excellence of contributions made by members of the medical profession in South Africa the presence of these visitors added both weight and lustre to the deliberations of Congress.

In the Western world cancer shares with circulatory diseases the rank of 'captain of the kings of death'. It looms large in the fears of mankind and during the last half century it has been the subject of intense medical and biological research. Surgery and radiology have successes to their credit in the treatment of certain forms of malignant disease, but it must be confessed that treatment has not yet begun to overtake the increasing mortality from the disease or to shake it from its place at the head of the list of killing diseases; and very little indeed is known about preventive measures.

A knowledge of etiology has enabled mankind to reduce many diseases that were at one time scourges of humanity to extinction or almost to extinction. The conquest of cancer in the fields of prevention or treatment must wait upon knowledge about its causation.

In view of the similarity in behaviour between the malignant cell and the embryonic cell attention has long been directed to the fundamental cytology and other biological problems of cell growth and proliferation, and to variations in these which may be observed under natural or artificially produced conditions. The action

of chemical and physical influences on embryonic and somatic tissues of various forms of life has therefore been the subject of intense study; and in this field much work has been focused on the effects of carcinogenic substances (under which heading carcinogenetic deficiencies may perhaps be included) and irradiation. Experiments in treatment have followed the same paths, naturally without waiting for full elucidation of the problems of etiology.

Such an elucidation still lies in the future—at what distance who can say? The results of scientific research often come suddenly like the sunrise. Professor Haddow in his contribution recorded here (page 1185) expresses the hope that we are at last approaching 'the end of the beginning'.

THE CYTOLOGICAL DIAGNOSIS OF CARCINOMA IN THE FEMALE GENITAL TRACT*

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The cytodiagnosis of carcinoma is by no means a new procedure. Francis Donaldson, in a paper published in 1853, described the cells seen in the 'cancer juice'. More than a hundred years ago Pouchet examined the cyclic changes in the vaginal epithelium. In 1861 Beale described cancer cells in the sputum from a patient suffering from carcinoma of the pharynx. Fifteen years later Quinke examined the cells of ascitic fluid, and a decade later Bahrenburg reported on the 'diagnostic results of the microscopical examination of the ascitic fluid in two cases of carcinoma involving the peritoneum'.

In 1943 Papanicolaou and Traut published their epic monograph entitled 'Diagnosis of Uterine Cancer by the Vaginal Smear'. The method has been severely criticized, strangely enough by eminent pathologists. In many instances this criticism has been most unfair, for no gynaecologist or physician who employs the cytodiagnosis of cancer claims that the method is infallible; they insist that the diagnosis must be confirmed by means of a biopsy. It is now accepted that cytological examination of vaginal smears is a valuable method in the diagnosis of cancer of the female genitract.

It has been stated that the method may give a false sense of security to the patient as well as to the doctor, when negative results are reported. This criticism may be true if one regards the cytological method as the only method to be used in the diagnosis of cancer. One must consider it only as an aid, and not as replacing histological methods. A negative smear does not necessarily mean that cancer is not present, just as a negative biopsy is not absolute proof that carcinoma is not present. Moreover, a positive vaginal smear should lead to a thorough examination and not to immediate therapy.

False positive reports may be brought about by several factors; there are numerous benign conditions in which the vaginal spreads contain cells which have malignant characteristics. Cells with extremely large hyperchromatic nuclei appear in smears from patients with chronic vaginitis. A large variety of cells normally found in the vagina arise from other parts of the genital tract; variations in these cells may be brought about by alterations of ovarian function, age, functional disturbances, inflammatory reactions and various benign growths. These variations may create confusion when one tries to evaluate the cells as suspicious of malignancy. Cervical polypi often present a problem in that numbers of cervical cells may be present, often of bizarre shape; but fortunately the nuclei nearly always have normal characteristics.

Trichomonas infection of the vagina gives rise to cells which may be identical with those characteristic of carcinoma *in situ* or of the pre-cancer cell complex described by Ayre. In the menopausal smear one often encounters cells which may easily be mistaken for malignant cells of the basal type.

The most vulnerable point in this field is the diagnosis of endometrial carcinoma. It is sometimes extremely difficult to distinguish between hyperplastic endometrial cells and those shed by a malignant process. Moreover, the tendency to exfoliate superficial cells is not so marked in endometrial as in cervical carcinoma; unless spreads are made from material aspirated directly from within the uterine cavity, no malignant cells may be found at all. For these reasons the accuracy rate for endometrial carcinoma of the endometrium is only about 75%, as compared with the 95% in cervical carcinoma.

Malignant conditions of the ovaries and fallopian tubes have been diagnosed by means of vaginal smears. Such cases, however, are very rare.

The advantages of the cytodiagnosis of carcinoma include the following:

1. It is a valuable ancillary method.
2. Differential diagnosis is provided between a simple erosion, a non-invasive carcinoma, and an early carcinoma.
3. A cytological test is cheaper than a biopsy.
4. A smear can be taken as part of a routine gynaecological examination.
5. In patients undergoing radiotherapy one can ascertain whether the growth is radio-sensitive or not. It may be ascertained whether there is a recurrence of the malignant process. Cases which have been subjected to radiotherapy usually present cervices which are very friable, and the taking of a biopsy may lead to an alarming haemorrhage.

* A paper presented in a symposium on the Etiology and Diagnosis of Carcinoma held in plenary session at the South African Medical Congress, Pretoria, October 1955.

6. In many cases the cervix arouses suspicion, yet one is unable to decide which area should be examined. In these cases, if biopsy is decided on, the so-called ring biopsy must be undertaken; and even when this is done the malignant spot may be missed unless great care is exercised by the pathologist. In these cases cytodiagnosis is most valuable.

7. The final advantage is that this method brings the possibility of an early diagnosis of malignancy within the scope of every doctor. If in his opinion there is anything suspicious about the appearance of the cervix, he is in a position to make the various smears and mail them to a cancer-detection clinic (assuming that such a clinic is available). The doctor's attention is thereby called to the existence of early recognizable cancer. One of the most useful contributions made by this method is the creating of a consciousness of early cancer on the part both of the doctor and the general public.

Questionable advantages that have been claimed for the method include the following:

(*a*) It has been suggested that it may be dangerous to take a biopsy in the presence of infection. Since, however, infection is present in almost all cases of carcinoma of the cervix, as a rule no bad effects are seen. Hence this is no reason for cytodiagnosis to supersede biopsy.

(*b*) It has also been suggested that it is useful in the diagnosis of post-menopausal bleeding. This is doubtful; unless the patient has come some distance to consult the gynaecologist, a curettage would be the procedure of choice.

Ayre has described cells which in his opinion are indicative of a condition he has termed 'pre-cancer cell complex'. One is led to understand that this condition precedes a carcinoma *in situ*. The characteristic cells are sometimes found in smears of patients suffering from trichomonas infection of the vagina. In view of this some have expressed the view that trichomonas infection may be a precursor of cancer in the cervix. Similar cells have been found in carcinoma *in situ*. However, if a biopsy is taken in a case with trichomonad infection, one finds that these cells originate from the surface layer and tend to migrate into the depth; whilst in carcinoma *in situ* the cells originate in the germinal layer and then spread to the surface. In trichomonas infection, the lesion is always reversible, but whether this reversibility obtains in all cases of true carcinoma *in situ* or those sometimes found in pregnant women, still remains to be proved.

Ruth Graham *et al.* have used vaginal smears to observe how cases of carcinoma of the cervix respond to treatment with radium. Changes in malignant cells as well as in normal cells indicate whether the growth is radio-sensitive or not. It will be impossible to include this aspect of cytology in the present paper.

PREPARATION OF VAGINAL SMEARS

It is imperative that no douche be used the night before the examination. As a rule 4 smears are made: (1) The secretion in the posterior fornix is aspirated by means of a glass pipette attached to a rubber bulb. The material collected is expressed on to a clean glass slide and spread evenly. The spread must not be too thick. Before it has a chance of becoming dry, the slide is placed in a jar containing equal parts 95% alcohol and ether. (2) The cervix is exposed by means of a non-lubricated speculum. The mucus in the cervical canal is aspirated and a spread is made with it and fixed like the previous one. (3) By means of a wooden spatula devised by Ayre, a scraping is taken from the whole squamo-columnar junction and a smear made and fixed as before. (4) An ordinary intra-uterine cannula with a fairly large bore and attached to a syringe is introduced into the uterine cavity. After moving the cannula around, some material is aspirated and a spread made in the routine manner.

Various other methods have been described. Some workers prefer to mix the aspirated material with 1 c.c. of the alcohol and ether mixture. This is then centrifuged and the sediment mixed with molten beeswax. When the wax is once more solid, sections are cut with a microtome and stained. Others advocate the sponge-biopsy method. A piece of jel-foam is placed in the posterior fornix and left in overnight. After removal the jel-foam is fixed in formalin and imbedded in wax, and sections are cut.

Different staining procedures may be utilized. Most cytologists still prefer the method described by Papanicilaou and Traut. The Hortega's silver-nitrate stain also gives good nuclear definition. Others maintain that the ordinary eosin and haematoxylin method gives equally good results.

NORMAL VAGINAL CYTOLOGY

In order to recognize abnormal cells in vaginal secretions the cytologist must have a good knowledge of the normal cells that may be encountered. The cells shed by the genital tract are (1) epithelial cells from the vaginal wall, (2) cells from the endocervix, and (3) endometrial cells from the uterine cavity. Other cells may be encountered, which do not have their origin from the vagina or uterus. The most important of these are (*a*) histiocytes, (*b*) giant histiocytes or foreign-body giant cells, (*c*) polymorphs, and (*d*) trichomonads.

Cells Originating from the Vaginal Epithelium

These cells originate from the 3 layers of the vaginal epithelium, viz. the basal layer, the layer of precornified cells, and the superficial layer or layer of fully cornified cells. Cells from the germinal layer of the vagina are never found in the vaginal smear.

The *basal cells* are the most immature of the epidermoid variety. They are round or oval. The cytoplasm is basophilic, staining blue-green, and as a rule the stain is intense. The nucleus is either round or oval, is situated centrally, is large in relation to the total size of the cell, and is usually clear and vesicular. These cells are present in cases of severe oestrin deficiency, e.g. after castration, after the menopause, *post partum* or during lactation. *Parabasal cells* are similar to the

basal cells, but bigger; they are more mature than the basal cells and lie superficial to them.

The precornified cells are still larger. They are flat, wafer-shaped, and of a hexagonal or octagonal outline. They take a blue or blue-green stain and the cytoplasm is clear. The nucleus is small and may be pyknotic. Cells from this layer represent what might be termed moderate oestrogenic effect.

The fully cornified cells are the fully matured cells. They are acidophilic, large and wafer-like, and hexagonal or octagonal in shape. The nucleus is small, centrally placed and pyknotic. Occasionally one finds fine chromatin granules around the nucleus or scattered throughout the cytoplasm. After irradiation or in the presence of infection, the cytoplasm may be filled with polymorphs.

Cells from the Endocervix or from an Erosion

As a general rule these cells are not found in the ordinary smear. They are only seen when the spread has been made from material collected by means of a surface biopsy. They are cylindrical in shape, with dark-staining nuclei. In many cases the cilia are still present. In the presence of chronic inflammation of the cervix, most of the cytoplasm may be absent and the nucleus may assume a hyperchromatic appearance, which frequently leads to confusion in interpretation.

Endometrial cells are also generally absent from vaginal smears. One only encounters them in smears taken just before or just after a menstrual period, or occasionally in postmenopausal smears. As a result of degeneration, very little cytoplasm is visible, appearing as little tufts on either side of the nucleus. The nucleus may be round or oval and presents a vesicular appearance.

Cells not arising from the Genital Tract

The histiocytes are the most important cells in this group, not only because they are very frequently seen in smears, but also because they so often present malignant characteristics and may thus cause considerable confusion. Two varieties are described:

(1) *The small histiocyte.* The cytoplasm stains very faintly and is vacuolated. The nucleus is bean-shaped, vesicular in appearance and situated at the periphery of the cell. Frequently this type of cell may assume larger proportions; the characteristics then remain the same except that it may have phagocytic properties.

(2) *The giant histiocyte* or the foreign-body giant cell. The cytoplasm is foamy in appearance and contains numerous vacuoles. It contains numerous nuclei similar to those seen in the other types of histiocytes. As a rule they are arranged along the periphery of the cell.

MALIGNANT CELLS

The most important general characteristic of malignant cells is the change in the cytoplasmic-nuclear ratio, due to the fact that the nucleus is unusually large in proportion to the size of the cell. The nucleus sometimes tends to grow far beyond normal limits and to acquire atypical forms. Its structure assumes a characteristic pattern with intensely stained granules or small clumps of chromatin and a distinct network of filaments centering on the nucleolus. Some nuclei show changes suggestive of the early prophasic stage of mitosis. Actual mitosis is rather rare. The nuclei are often hyperchromatic as the result of degeneration; degenerating nuclei may entirely lose their finer structure and stain almost black. Another feature is that the nucleus often shows atypical and unequal fragmentation, resulting in the not infrequent appearance of binucleate or multinucleate cells. In many instances macronucleoli are seen. This feature, however, is not a definite characteristic of malignant cells, since it may be seen in cells originating from innocent neoplasms. When malignant cells appear in clusters they offer additional criteria; one of these is crowding of the cells, which is of definite diagnostic value.

Squamous Carcinoma. The cells desquamated by epidermoid carcinoma of the cervix are of two varieties, namely differentiated and undifferentiated. In differentiated cells the cytoplasm is well defined, with well-formed cellular borders. In the undifferentiated cells the cytoplasm is not altogether clear and the borders are ill-defined. Three main types of differentiated cells are described:

1. The most mature type of differentiated cell resembles the basal cell, with the exception that the nucleus is hyperchromatic and the cytoplasmic-nuclear ratio is abnormal.

2. The fibre cell, which is elongated, with an elongated hyperchromatic nucleus.

3. Bizarre types of cell, including the tadpole cell, which consists of a head with a hyperchromatic nucleus and a tail, the spider cell, and monster cells such as the multinucleated giant cell, which has numerous hyperchromatic nuclei, cytoplasm staining a dark crimson colour, and as a rule large well-defined vacuoles.

Malignant Endometrial Cells. The variation in size of individual cells is not as great as in carcinoma of the cervix. The cells are usually seen in clumps. Little cytoplasm is present or, should there be a fair amount, it usually contains vacuoles. The nuclei are hyperchromatic and the chromatin may stain as dark granules in the nucleus.

Carcinoma in Situ. Neither biopsy nor smear diagnosis will alone reveal all cases of carcinoma of the cervix, but by combining the two methods a correct diagnosis may be made in 98% of cases. Many workers are of the opinion that a surface biopsy is the ideal method for detecting carcinoma *in situ.* Some, however, feel that it is impossible to diagnose the condition by means of cytology; there may be cells indicative of carcinoma *in situ,* but often one finds smears containing these cells as well as those pathognomonic of invasive carcinoma.

The characteristics of the cells found in pre-invasive carcinoma are as follows:

1. The number of malignant cells obtained in the presence of carcinoma *in situ* is variable. The initial specimen may contain numerous characteristic cells,

whilst subsequent examinations at intervals of several weeks commonly show few characteristic cells. This may be due to the fact that most of the area involved has been removed by the first scraping; the presence of fewer cells must not be put down to the fact that the lesion is healing or that the presence of these cells merely indicates an inflammatory process. In general, tissue spreads containing only a few cells believed to be derived from a carcinoma *in situ* must be viewed with suspicion and great caution; repeat spreads should be requested. Proliferating parabasal cells may resemble cells from a carcinoma *in situ*.

2. They are usually larger than invasive cancer cells and have a greater amount of cytoplasm, which stains a typical orange yellow.

3. The nuclei may be either small, hyperchromatic, without detail, and with very irregular nuclear membrane; or they may be large, foamy and agranular, with well-defined or ill-defined borders.

4. On the other hand the nuclei may be found with distinct borders and a particular type of granularity which is never found in cells from an invasive carcinoma.

5. Bizarre forms, or multinucleated giant cells characteristic of invasive carcinoma, are rarely found in smears when the growth is in the pre-invasive stage.

6. Exfoliated cells from a carcinoma *in situ* generally appear singly or loose in groups, but never in clusters adherent to each other.

7. The cells are only slightly variable in size, and lack the marked pleomorphism so characteristic of cells from the more differentiated squamous-cell carcinomas. In size and shape they are comparable to the normal parabasal cells.

8. The nuclear-cytoplasmic ratio is less variable than in other malignant neoplastic cells although, rarely, it may be seriously altered.

Pre-invasive Cancer Cell Complex. Changes may be found in the various cells of the vagina:

Superficial Cells. The changes in these cells are threefold:

1. Cellular enlargement, defined as a proportional increase in the size of the cell as well as in the nucleus, with no change in the cytoplasmic-nuclear ratio.

2. Multinucleation may be seen in a few cells. The nuclei may be 2 in number, rarely 3, and very rarely 4. Hyperchromatism as a rule is never present.

3. Keratinization of the cytoplasm (occasionally) showing by yellow staining with the Papanicolaou stain. At no time does this affect the nucleus, as is frequently the case in leukoplakia, in which the process of keratinization changes the cell into a cell with a ghostlike appearance with only a poorly-outlined or absent nucleus.

Parabasal Cells. These may be enlarged, the cytoplasm may be vacuolated and multinucleation may also be encountered.

Endocervical Cells. No changes have been noted in these.

SUMMARY

The advantages and disadvantages of cytodiagnosis of cancer are described. The various methods of preparing the material for examination and the methods of staining are noted. The essential differences between normal and abnormal cytology are outlined. Attention is also drawn to the application of the method in diagnosing premalignant conditions of the cervix.

THE AETIOLOGY OF PRIMARY CARCINOMA OF THE LIVER—WITH SPECIAL REFERENCE TO THE BANTU RACES OF SOUTHERN AFRICA*

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Primary carcinoma of the liver, perhaps the most challenging cancer problem in Africa and Asia, is a remarkable form of malignancy not only because of its demographic, geographic, sex and age distribution, but also because of the ease with which it can be induced in experimental animals with compounds of known chemical composition.

GEOGRAPHIC AND DEMOGRAPHIC DISTRIBUTION

A survey of the world's available post-mortem statistics has indicated that the incidence of primary liver cancer varies strikingly among the different races of mankind.[1]

Of rare occurrence among the peoples of Western Europe and North America, it is by contrast remarkably common among the inhabitants of Africa and certain parts of Asia.

Geographically, the areas of known or suspected high prevalence of the disease extend from the West African coast along the south-eastern and eastern portions of Africa, across eastern and south-eastern Asia, to and including particularly Indonesia, the Philippines, China and Japan.

Western Races. Primary carcinoma of the liver is rare among all Western people, irrespective of whether they live in Europe, America, Africa, Asia or elsewhere. The post-mortem rate was 0·1% in Europe and 0·3% in the United States of America; and the relative frequency of primary liver cancer to all other carcinomata

* A paper presented in a symposium on the Etiology and Diagnosis of Carcinoma held in plenary session at the South African Medical Congress, Pretoria, October 1955.

was 1·2% in Europe and 2·5% in the United States of America.

African Races. Primary liver cancer, on the other hand, is extraordinarily common among the Bantu and other aboriginal races inhabiting the vast territories south of the Sahara Desert, including South Africa,[1–8] Portuguese East Africa,[9–10] Southern Rhodesia,[11] Kenya,[12] Tanganyika,[13] Uganda,[14–16] Belgian Congo,[17] Nigeria[18–20] and French West Africa.[21–24] In such widely separated areas as Lourenço Marques in Portuguese East Africa [9–10] and Dakar [22–24] on the French West African coast it is, indeed, by far the most frequent form of internal cancer encountered in male Africans.

The post-mortem rate, according to the reported statistics, averages 0·8%, although rates of 1·9%[4] and 2·6%[25] have been registered at the Johannesburg non-European Hospital. The relative frequency of primary liver cancer to all other carcinomas at autopsy has been found to vary between 30 and 50% in different localities. Moreover, among the migratory Bantu labourers of the Witwatersrand gold mines (a specially selected and fit group of young men who hail from various tropical and sub-tropical regions) primary liver cancer was responsible for practically 90% of all carcinomata;[1, 26] whilst in the young West African soldiers stationed in Nigeria during the last war this disease accounted for almost 70% of all carcinomas.[20]

Oriental Races. There must be some factor which is common to the livers of Bantu and Oriental races but is absent or less operative in those of the Western races, since among some Oriental people the frequency of primary carcinoma of the liver is sometimes as high as in the Bantu.

A high incidence of primary liver cancer has been found among Indonesians, Filipinos, Chinese and Japanese. Scattered reports of an enhanced incidence of the disease have at different times also come from India, French Indo-China, Formosa and Korea.

The post-mortem rate for Asia, according to available statistics was 0·76% and the percentage frequency of primary liver cancer to all other carcinomas at autopsy was 13·9.

In Indonesia[27] the post-mortem rate was 1·3%, and the percentage frequency of primary liver cancer to other forms of malignancy was 79·3 for male Javanese, 31·5 for male Chinese, and 6·2 for female Javanese. Moreover, at the Queen Mary Hospital in Hong Kong it is the most common malignant tumour encountered in in-patients.[28]

Sex and Age Incidence. Primary liver cancer occurs predominantly in males. Among Africans and Indonesians the disease is pre-eminently one of youth, occurring chiefly under the age of 40 years; in other races it is commonest in or after middle age and is rare before the age of 40 years. No age, however, is exempt, for the tumour has been discovered in children of all ages; more than 100 such cases from the literature have been tabulated and discussed at different times.[29,30]

ENVIRONMENTAL FACTORS IN AETIOLOGY

The true cause of primary liver cancer (like that of cancer in general) is unknown. It is becoming increasingly apparent, however, that environmental factors may play a vital role in the aetiology. Indeed, few fields of experimental cancer research have yielded more striking results than the production of primary liver cancers in laboratory animals with the azo-compounds (e.g. 'butter yellow'—p-dimethylaminoazobenzene), with aminofluorene, or with other chemical compounds of known composition, which are specifically carcinogenic for the liver and whose actions are controlled to some extent by dietary factors, including proteins and vitamins of the B-complex.

It is highly improbable that a common genetic factor is responsible for the enhanced incidence of primary liver cancer among such diverse and widely separated people as the indigenous races of Africa and the Orient. Moreover, there is strong presumptive evidence that the frequency of this disease varies with environment even in the same race; on the Witwatersrand gold mines, for example, primary liver cancer was found to be almost 6 times as frequent in Bantu miners from Portuguese East Africa as in those from South Africa although there is little, if any, genetic difference between them.[1, 26]

The remarkable early age-incidence of the disease in Africa and Indonesia suggests that the cause of the malignancy in susceptible races is one which may begin to operate at an early stage of life.

Cirrhosis of the Liver. Cirrhosis of the liver, on account of its frequent association with primary liver cancer and its high incidence among the very races known to be prone to this tumour, is commonly regarded as an important precursor of the malignant process. On this account, a number of known cirrhosis-producing agents, which are sometimes found in close association with liver cancer, have at different times been credited with carcinogenic properties.[1] These cirrhotic agents include intestinal parasites[31] and liver flukes[28] (which are stated to elaborate substances that are toxic for the liver); schistosomiasis (which produces fibrosis of the liver around embolized schistosome ova);[5] hydatid cysts; highly spiced foods; syphilis; selenium; alcohol; infective hepatitis;[23] haemochromatosis and siderosis,[32,33] and a keloid diathesis in negroid races, amongst whom there is often a tendency towards excessive connective-tissue hyperplasia, even after seemingly unimportant wounds. Not one of these agents, however, is common to all the communities known for their high incidence of primary liver cancer.

Malnutrition (Kwashiorkor) and Cirrhosis. It would appear, however, from clinical and experimental observations, that faulty diets are perhaps the important and commonest factors in the production of cirrhosis and other liver damage. Moreover, a recent survey has indicated that the geographical areas in Africa and Asia which register high frequencies of primary liver cancer are also those with poor nutritional standards.[34]

The defects common to the dietaries of these poorly nourished localities are insufficiency in animal and other first-class proteins and in certain vitamins, and excess of carbohydrates. Chronic malnutrition is as a consequence rife here and often manifests itself at a very early age as an acute (and sometimes fatal) form of 'kwashiorkor'—a nutritional syndrome that was originally reported from the Gold Coast about 20 years

ago, but has since been described in different parts of the world under a variety of names, including 'infantile pellagra' in South Africa.

Kwashiorkor. Kwashiorkor (a West African term referring to the reddish tint of the hair in African children noted during the time of weaning) is mainly due to the lack in the diet of animal proteins and (in certain areas) of vitamins of the B-complex. It affects children during the late breast-feeding, weaning or post-weaning periods, i.e. between the ages of 6 months and 3 or 4 years. The main clinical features include oedema, associated with low plasma-proteins and sometimes with ascites; retardation in growth and muscular wasting; diarrhoea; various dermatoses; angular stomatitis; cheilosis and glossitis; dyspigmentation of the skin; depigmentation and loss of texture of the hair; lethargy or irritability; anaemia; atrophy of the pancreas; and enlarged fatty livers, which in later life may become fibrotic and culminate as a profound form of portal (Laennec) cirrhosis. It is these liver lesions, initiated as they are in early childhood, that appear to make kwashiorkor such an important factor in the aetiology of primary liver cancer.

The histological appearances of the fatty and fibrotic livers of kwashiorkor resemble closely those produced in rats fed on the staple Bantu diet of corn (maize) meal and sour milk,[35] and also those of rats fed on experimental diets deficient in the lipotropic factors, methionine or choline.[36,37] Moreover, liver cancer has already been induced in experimental animals by the sole means of choline-deficient diets.[38]

DISCUSSION

It must be remembered, however, that most of the evidence pertaining to aetiology is circumstantial, and that the underlying cause for the remarkable sensitivity of the Bantu liver to cancer has not been established. Neither the evolution of cirrhosis from kwashiorkor nor the exact mode of neoplastic transformation from active cirrhosis is as yet understood. A great deal of research is obviously necessary.

In cirrhosis, perhaps other environmental factors (additional to malnutrition) are required to effect carcinogenesis; a susceptible Bantu liver deranged by the ravages of malnutrition may in this way become more vulnerable to some of the external stimuli already mentioned—including endemic parasitic infestation and irritation by known toxic substances—or perhaps to some as yet undiscovered compounds with carcinogenic potentialities.

No naturally occurring carcinogenic substances (analagous to 'butter yellow' or other compounds used for the production of liver cancer in experimental animals) have been reported thus far in the few available enquiries into the dietaries, customs and habits of malnourished populations. Intensive investigations in South Africa for likely carcinogens are therefore highly desirable, but these should be conducted in the immediate environments of those Bantu populations registering the highest rates for primary liver cancer, as may be determined by modern statistical methods.

The solution in South Africa of the mystery surrounding primary liver cancer will certainly have profound effects on the whole problem of cancer. Research into the causation, prevention and cure of this unique form of cancer is without doubt one of the principal contributions which can and should be made by South African medical science.

SUMMARY AND CONCLUSIONS

1. Primary carcinoma of the liver, one of the most challenging medical problems in Southern Africa, is very rare among all Western people, whereas it is relatively common in African and in certain Oriental races, among whom it is often more than 40 times as frequent as in Western people.

2. In the young Bantu employed on the Witwatersrand gold mines, primary liver cancer accounts for almost 90% of all carcinomata; among them it is almost 6 times as frequent in those from the East Coast (Portuguese East African) as in those from South Africa.

3. Primary liver cancer is pre-eminently a disease of males; in the Bantu it has most often been described in young adults.

4. Although the true cause of primary liver cancer, like that of cancer in general, is unknown, it is becoming increasingly evident that environmental factors play an important role in the aetiology. Primary liver cancer can be readily induced in experimental animals by chemical compounds of known composition.

5. Cirrhosis of the liver, on account of its frequent association with primary liver cancer, is commonly regarded as an important intermediate stage in the evolution of the tumour.

6. Experimental work and clinical observations have indicated that faulty diets, especially deprivation of protein and vitamin-B complex, as occurs in the syndrome 'kwashiorkor', are perhaps the most common causes of cirrhosis in populations susceptible to primary liver cancer.

7. Other cirrhosis-producing factors sometimes found associated with primary liver cancer include parasitic infestation, infective hepatitis, and haemochromatosis, and these may enhance the effects of malnutrition on the liver.

8. Intensive research in South Africa into the causation, prevention and cure of primary liver cancer is advocated.

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THE BANTU AND THE AETIOLOGY OF CANCER*

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The object of this short article is to present South Africa's contribution to the solution of the problem of the aetiology of cancer. For the clinician, the hunt for the aetiology of cancer is synonymous with the search for a cure, and the two lines of research must run parallel and will probably reach their goals at the same time.

Despite all the work that has been done, and is being done, all over the world, the final goal seems as far off as ever; but various signposts are appearing in all sorts of places, and South Africa, with its unique opportunities in this field, should be instrumental in creating important new signposts. It is not out of the question that the final goal, as in the realms of anthropology dealing with the origin of man, will be reached on South African soil.

The past can only be dealt with by the mention of a few names. The pioneer work of de Ligneris, who in 1927 made the first rather primitive statistical survey of malignant conditions in the Bantu, and later investigated the carcinogenetic properties of Bantu livers, must be mentioned first; Professor Sutherland-Strachan and his work on liver pathology; Dr. B. J. P. Becker and his team of workers; Dr. James Murray and his colleagues at the South African Institute for Medical Research, all of whom have made valuable contributions to the picture of malignant conditions in the Bantu; the Gillman brothers, whose contributions are of world renown; Dr. C. Berman, whose observations on primary carcinoma of the liver have proved invaluable; and others.

What of the present? Most of these workers are continuing with their contributions, and we have in addition the work of Dr. A. G. Oettle and Dr. J. Higginson in the Cancer Research Unit of the S.A.I.M.R., who are making the first scientific statistical survey of the distribution of malignant conditions in a sample urban Bantu population. They have already shown how erroneous some of our past clinical impressions have been, but have confirmed others, and many signposts for research can be anticipated from their survey. Some valuable work is being done in the Radiotherapy Department of the Johannesburg Hospital, where accurate figures have been kept since 1949 and comparative series in various regions of the body have shown suggestive racial differences, indicating possible lines of research. For example, in 1953 in a routine annual survey it was noted that carcinoma of the paranasal sinuses appeared relatively common in the Bantu, and a subsequent investigation showed that almost all these cases occurred in heavy snuff-takers.

TABLE I. RELATIVE PROPORTIONS OF HYDROCARBONS (PYRENE AS UNITY)

Hydrocarbons	*Zulu Snuff*		*Venda Snuff*		*Cigarette Smoke Condensate*	*Chimney Soot*
	(1)	(2)	(1)	(2)		
Anthracene	0·12	0·09	—	0·11	1·0	0·2
Fluoranthene	—	1·4	1·5	1·6	—	1·3
3 : 4 Benzpyrene ..	0·43	0·48	—	—	0·1	0·55
1 : 12 Benzperylene ..	—	0·25	—	—	—	0·35

(Pathology Department, St. Bartholomew's Hospital, London.)

Further enquiries showed that the Natives of South Africa do not use the ordinary tobacco snuff, but add various herbal mixtures which are previously incinerated. Analysis of some of these additives have revealed carcinogenetic agents more potent than those in cigarette-smoke condensates; in fact it would appear that we are

* A paper presented in a symposium on the Etiology and Diagnosis of Carcinoma held in plenary session at the South African Medical Congress, Pretoria, October 1955.

dealing with a type of chimney-soot cancer (see Table I). This work will shortly be published.

To discuss all racial differences noted in the manifestations of malignancy would take up too much space and it is only possible to give a list of the main differences which have been noted so far and appear worth investigating.

In the *digestive tract* it has been known for many years that primary cancer of the liver is almost the prerogative of the Bantu, but the fact that carcinoma of the oesophagus is relatively frequent in the Bantu, and that of the stomach correspondingly rare, has only recently come to light, and certain differences in the manifestations of cancer of the tongue should bear investigation. The *cutaneous system* has naturally shown clinical differences on account of the differences in pigmentation, but the bizarre pattern and manifestations of skin cancer in the Bantu should give aetiological clues apart from the effect of actinic rays, and the albino should be a source of much useful information. *Melanomata* have a markedly different clinical course in the Bantu and, except in the albino, behave like carcinomata with slow lymphatic spread. *Kaposi's haemangiosarcoma* though not strictly a cutaneous malignancy, is mainly cutaneous in its manifestations, and investigation of this condition, so markedly more common in the Bantu, might produce useful information on the aetiology of cancer. In the *respiratory tract* mention has already been made of the relative frequency of cancer in the nose and paranasal sinuses, and studies of the transitional changes could easily be made. Finally in the *genito-urinary tract* marked differences have been noted.

What is to be done with all this wealth of clinical material? Those of us who have studied the Bantu for the last 25 years have noted rapid clinical changes, not only in the field of malignancy, but in most medical and surgical manifestations. One need only mention diabetes, hyperthyroidism, duodenal ulcer and appendicitis, which were very rare in the Bantu 20 years ago, and which can now be found in almost every medical and surgical ward. Renal calculi, unknown 20 years ago, now appear, infrequently it is true, but sufficiently to have to be taken into account in making a diagnosis.

The more research work that is being done, the more obvious it is becoming that environmental factors, rather than genetic differences, are at play in most instances. Environmental factors—diet, smoking and other habits, levelling up of socio-economic conditions—are all tending to make aetiological factors more equal, and in another generation the opportunity of studying the clinical racial differences will be lost. The importance of the changing clinical picture cannot be stressed sufficiently, and must be taken into account in our campaign against cancer. South Africa is the only country on the African continent with the material available and the finances, personnel and institutions capable of carrying out the necessary work.

The first step must be an extension of the work done by Dr. Oettlé and Dr. Higginson on a national basis. The scope of their work is too limited to be of great value and must be extended to include various tribal groups and rural areas. The next step must be the formation of a Central Cancer Institute for Non-Europeans, preferably in Johannesburg, where the nucleus for this type of work is already present, but it must be closely associated with the S.A.I.M.R., the Medical School, and the provincial hospitals. Suitable cases would be sent to the proposed institute by the various teams undertaking demographic research in locations, reserves and other sample areas. The latest tendency in the search for the aetiology and cure of cancer seems to be the study of the host, rather than the tumour, and in this South Africa has an ideal opportunity. Most of the manifestations of malignancy in the Bantu are superficial and accessible, e.g. melanoma, Kaposi's disease, sarcoma, antral disease etc. In an institute as suggested new forms of treatment could be tried out under scientific supervision—the host could be studied—the tumour reactions could be assessed; in fact such a set-up would be unique. Treatment must of course be the prime object of this institute, but with the co-operation of the Physiology, Pathology and other departments, and the S.A.I.M.R., invaluable information could be gleaned, and instead of the haphazard efforts of many individuals working under difficult conditions, we should have a coordinated team dealing with these problems under relatively ideal conditions.

It is my firm conviction that some of the clues of the cause of cancer and, as a corollary, its cure lie in our work with the South African Bantu and that with the correct approach South Africa could easily lead the world in the conquest of cancer; but we must make our efforts before it is too late.

MALIGNANT DISEASE IN CHILDREN*

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Malignant disease in children is a rare condition. In the children's hospitals of England and of the United States only about 0·5% of the admissions are cases of malignant disease. But although the incidence is low, cancer is an important cause of death in childhood.

Figs. 1 (*a*) and 1 (*b*) show the causes of death from birth to 14 years, contrasting 1939 with 1953. This abridged account omits deaths from accidents and violence, but illustrates the changing importance of certain diseases in Great Britain. There has been an immense decrease in deaths due to the infectious fevers, gastro-intestinal infections and tuberculosis. On the other hand, the death rate from malignant disease has risen in 14 years from

* A paper presented in a symposium on the Etiology and Diagnosis of Carcinoma held in plenary session at the South African Medical Congress, Pretoria, October 1955.

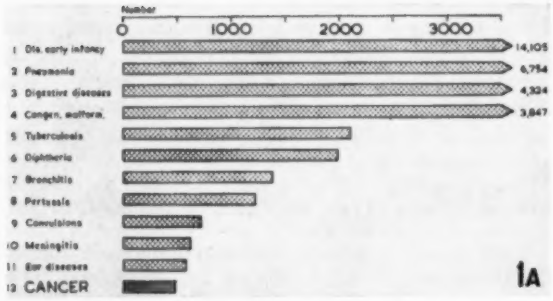


Fig. 1 (*a*). Children's deaths 0-14 years: 12 leading causes (excluding accidents and violence): England and Wales 1939.

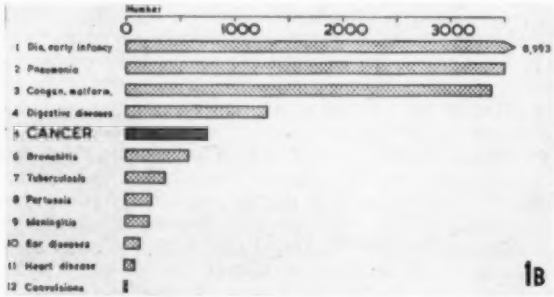


Fig. 1 (*b*). Children's deaths 0-14 years: 12 leading causes (excluding accidents and violence): England and Wales 1953.

the 12th to the 5th position in the order of frequency. If we consider instead the causes of death in children between 1 and 14 years, i.e. excluding infants, malignant disease heads the list (Fig. 2). It has now, in addition, pride of place even over automobile accidents.

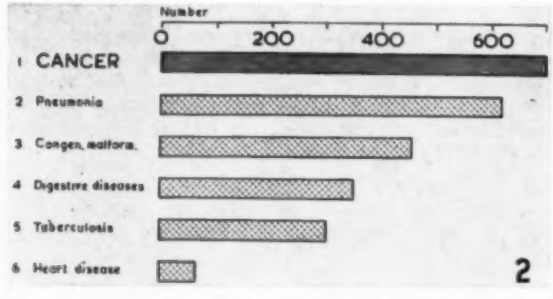


Fig. 2. Children's deaths 1-14 years: 6 main causes (excluding accidents and violence): England and Wales 1953.

These facts are surely adequate to recommend a special study of malignant disease in children, not only to investigate its occurrence and its possible causes but to diagnose and to treat it adequately.

In my own corner of England, the North-West Region, we have now two organizations for the study of cancer in children—the Christie Hospital, and a Children's Tumour Registry. The older of these is the radiotherapy treatment centre at the Christie Hospital in Manchester. At this centre are treated all the cases of malignant disease which are suitable for radiotherapy from a population of 4½ million. Every year we see and treat between 50 and 60 cases occurring in children.

One of the most interesting aspects of children's tumours is the study of the pathology and of those factors which may determine the incidence. For this study we have established a Children's Tumour Registry for the same north-west area of England. The Registrar, who is a paediatrician, is attempting to follow every case of cancer occurring in children in all of the hospitals of the region. Since many children's tumours are rare or atypical, we have inspanned the help of a panel of pathologists to review the histology of each case. We are also interested in the family history and in the blood groups, both of which may enlighten us on genetic factors.

It is not only important to study and to treat malignant disease in children, it is important to treat them as children and not as small adults. One of the reasons for this viewpoint is illustrated in Table I, which shows the very different site-distribution of tumours in the child and in the adult. The figures have been obtained by comparing the relative distribution of sites and types of cancer referred for radiotherapy at the Christie Hospital. They do not, therefore, include the purely surgical

TABLE I. MALIGNANT TUMOURS IN CHILDREN AND ADULTS: DISTRIBUTION BY SITES

Based on 4421 registrations at Christie Hospital in 1953

Site	*% in Children*	*% in Adults*
Lymphatic and Haem. Tissue	22·9	4·3
Brain and Cord	20·8	0·6
Abdomen (Kidney, Adrenal, Testis, Ovary, Pancreas)	25·0	3·0
Connective Tissue & Bone	12·5	1·5
Orbit	8·3	0·1
Melanoma Skin	4·2	0·8
Skin other than melanoma	0	25·4
Breast	0	25·4
Uterus	0	11·0
Mouth and Lip	0	6·4
Various	6·3	21·5

types such as the large group of gastro-intestinal neoplasms. These are extremely rare in children and enhance the differences still further. In the adult, we find the heavy percentages in the accessible cancers—skin, breast, uterus and mouth—and these do not appear in the children's list. In the children's list we find the heavy percentages in the malignant reticuloses, and in the tumours of the brain and cord, of the abdomen, of bone, and in the orbit; these tissues provide only a small fraction of the tumours in the adult.

Although the preponderance of tumours in the different sites is so different in children and in adults, yet the nature of many tumours is common to both. Where this is the case, the treatment is largely the same whatever the age, except for the special interest in protecting growing tissue. I am mainly concerned with those features which are peculiar to children and I will not, therefore, stress treatments which fall into line with general radiotherapy practice.

I propose, therefore, dealing briefly with four of the larger groups of tumours shown in Table I, and I will pick my illustrations of treatment from those tumours which occur rather particularly in childhood.

THE RETICULOSES

On the basis of the registrations of our Children's Tumour Registry, the largest group of tumours occurring in children is that of the reticulo-endothelial system—the leukaemias, Hodgkin's disease and the sarcomas of lymphoid and reticulum cells. They are not peculiarly children's tumours in spite of their preponderance. Of the malignant reticuloses, the most frequent is acute leukaemia, and the age-incidence is a point of interest. There is a high incidence in the 0-4 age group and this is shown in Fig. 3 to be due to a peak between 2 and 3

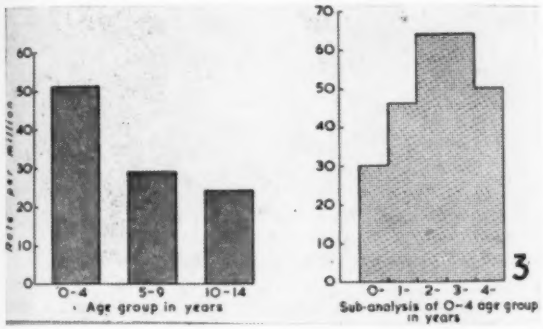


Fig. 3. Leukaemia mortality in children: England and Wales 1953.

years. There has been an attempt to correlate it with the incidence of measles at this age, but so far there is no real evidence of a connection. One of the differences in the outlook for acute leukaemia in the child and in the adult is the present-day optimism which has been engendered by the effects on the disease in children of the antimetabolite drugs and of the hormones cortisone and ACTH. The average survival time used to be about 5 months; it is now more than doubled, but the treatment is still unfortunately only palliative. Hodgkin's disease and other generalized reticuloses are treated with radiotherapy and by chemotherapy, like the same conditions in the adult, and the effects are similarly palliative.

The only curable type of reticulo-endothelial tumour in children or in adults is the lymphosarcoma or reticulum-cell sarcoma which has not yet generalized. This tumour occurs not infrequently in the tonsillar region and in this site it can be treated successfully by regional irradiation which includes the neck nodes.

BRAIN TUMOURS

The 2nd largest group recorded by the Children's Tumour Registry is the tumours of the central nervous system. The types of brain tumours seen at the Christie Hospital are probably not strictly representative of the actual distribution because we do not see those cases of astrocytoma or haemangioblastoma which have been successfully removed by the neuro-surgeon. We see tumours which either cannot be removed or which are not suitable for surgical treatment. This classification, shown in Table II, gives an idea of the types of brain tumours referred for radiotherapy. The medulloblastoma of the cerebellum, which heads the list, is truly a

TABLE II. CHILDREN'S TUMOURS: CLINICAL DISTRIBUTION OF BRAIN- AND SPINAL-CORD TUMOURS REGISTERED 1945–52

Description	*Brain*		*Spinal Cord*	
	No.	*%*	*No.*	*%*
Medulloblastoma	25	35%	0	0
Astrocytoma	14	20%	0	0
Glioma/Glioblastoma ..	5	7%	1	17%
Ependymoma	5	7%	2	33%
Meningioma	2	3%	0	0
Sarcoma, lepto-meningeal	1	1%	0	0
Sarcoma	0	0	2	33%
Oligodendroglioma ..	1	1%	0	0
Indeterminate	19	26%	1	17%
	72		6	

children's tumour because it is rare in the adult. It is in a class by itself in its pathology and its treatment, which is exclusively radiotherapeutic. I shall return to it later. The remainder, the astrocytomas and glioblastomas, are similar in their pathology and in the technique of treatment to the same tumour occurring in the adult, with the difference that in children these tumours are more commonly found below the tentorium. Table II also shows the relative rarity of tumours occurring primarily in the cord.

In the treatment of a brain tumour in a child, it is necessary first to consider whether it is possible to cure the tumour. If the answer is 'yes' it is essential to spend a great deal of time and trouble in planning a radiation technique which will deliver an adequate dose to the whole tumour. This is illustrated by the treatment of the *astrocytoma*. In many cases the treatment of an astrocytoma is properly surgical and complete removal is cure. However, if the tumour cannot be removed completely because of inaccessibility, there is still a reasonable hope of cure by radiotherapy. The astro-

Fig. 4. Beam-directed irradiation of an infratentorial brain tumour (astrocytoma).

cytoma is not very radio-sensitive; so success depends on the accuracy of delivering a considerable dose of radiation. A large dose must be limited to a small volume of the brain and so the curable tumour is a small one.

In Fig. 4 is shown the technique designed to irradiate an astrocytoma occurring below the tentorium in a little girl. The tumour was accurately localized by the neurosurgeon but could not be removed. This particular plastic helmet has 4 wax seatings to direct the X-rays in such a way that 4 beams of radiation will converge on the tumour, while the normal tissues get the least possible irradiation. The treatment requires daily radiation over 4-5 weeks. Boys and girls love wearing these beam-directing helmets, especially nowadays when they can regard themselves as space-men. The results of radiotherapy in the treatment of astrocytomas is shown in Table III. At 3 years there is a 47% survival and at 5 years it is nearly the same. I think we can properly regard these children as cured, for we have followed a number of them for much longer periods.

TABLE III. CHILDREN'S TUMOURS: ASTROCYTOMA OF BRAIN (PATHOLOGY PROVEN): 3-YEAR AND 5-YEAR RESULTS OF CASES TREATED BY RADIATION 1932–51

Treated	*Survival Rate*	*Period*
17	47%	3-year
12	42%	5-year

In the curable group I would also place the haemangioblastoma, which we rarely see because of the success of surgical removal. The occasional ependymoma is also curable. We have not been successful in curing either the oligodendroglioma or the glioblastoma multiforme.

One of the most rewarding tumours to treat is the *medulloblastoma* of the cerebellum. This tumour was described and named by Bailey in 1925, and it was of this tumour that Bailey said that surgery was not only futile but contra-indicated. Nevertheless, the neurosurgeon is an essential colleague of the radiotherapist, not only in obtaining the biopsy material but in reducing the symptoms by decompression. This truly embryonic tumour occurs more commonly in boys. It arises in the cerebellum and, unlike the other brain tumours, it spreads forward on the surface of the brain and backwards along the membranes of the cord, where it surrounds the cord like a collar (Fig. 5*a*). We have had three cases with metastases in distant bones. The histological appearances are shown in Fig. 5 (*b*); the pattern of cells is fairly characteristic and mitoses are frequent.

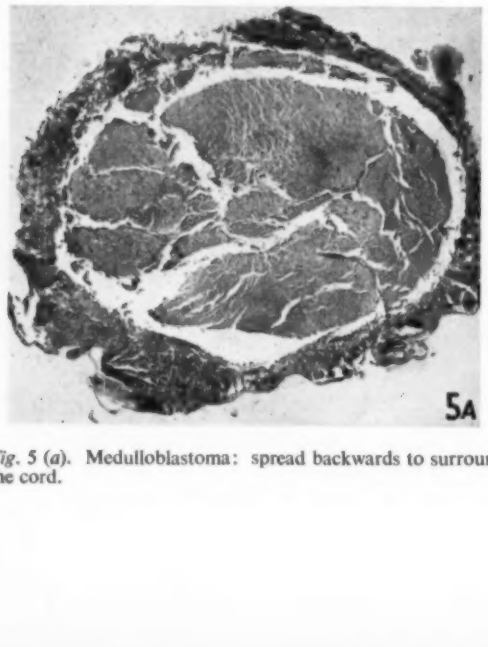


Fig. 5 (*a*). Medulloblastoma: spread backwards to surround the cord.

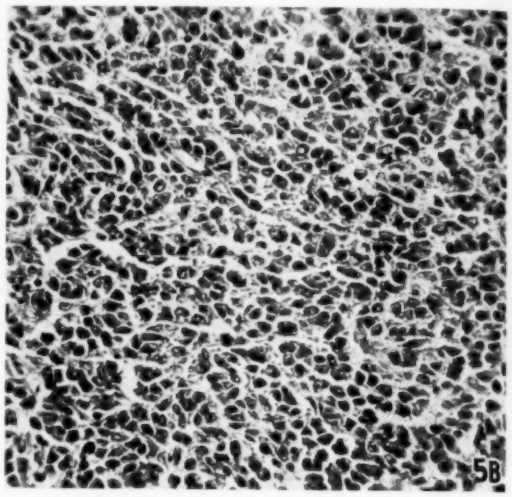


Fig. 5 (*b*). Medulloblastoma: histological pattern.

The patients have a history of ataxia, headache and vomiting. They invariably show papilloedema or some degree of optic atrophy. There is nystagmus and usually a 6th-nerve paresis.

The tumour is highly radio-sensitive. X-radiation must be applied homogeneously to the entire central nervous system, including the brain and cauda equina. Because of the awkward shape of this volume the treatment is rather elaborate. The posterior part of the head and the entire length of the spinal canal are treated by a single long X-ray field. The spinal part of the field is limited at each side with lead of sufficient thickness to protect the remainder of the trunk. It is necessary to support the lead over the child and this is done by incorporating the lead in a table which has a central slot through which the X-ray beam passes (Fig. 6). This treatment is given daily over about 3 weeks and delivers a dose of 3,000 r to the cord and the posterior part of the head. However, the dose given in this way is inadequate to treat the whole of the head, and so it is supplemented with front X-ray fields which are designed to ensure that the irradiation throughout the brain is homogeneous.

We find that the children are most cooperative in this somewhat tedious treatment. This is partly because they themselves feel so much better in a very few days; the completely ataxic child can feed himself, or walk, when before he was quite helpless. At the end of treatment the child is immeasurably better. He has a temporary

Fig. 6. Medulloblastoma: irradiation of posterior field.

epilation of the head and a moderate erythema of the skin over the spine.

The results of this treatment are shown in Table IV. It will be seen that the survival rate is 56% at 3 years and 42% at 5 years. This difference in survival rate shows that it is possible to get recurrence of the primary tumour even after several years. However, a number of our children have now been well for over 10 years; some are grown up; one girl is married, one boy is a practising lawyer. The prognosis for girls with medulloblastoma is better than it is for boys and the late recurrences seem to happen more frequently in boys. I do not think that the better prognosis in girls is due to an earlier diagnosis. I think that the tumour is more curable in the sex with the lower incidence—in this case, in the girl.

TABLE IV. CHILDREN'S TUMOURS; MEDULLOBLASTOMA OF BRAIN (PATHOLOGY PROVEN): 3-YEAR AND 5-YEAR RESULTS OF CASES TREATED BY RADIATION 1932-51

Treated	*Survival Rate*	*Period*
27	56%	3-year
19	42%	5-year

PRIMARY TUMOURS OF THE ABDOMEN

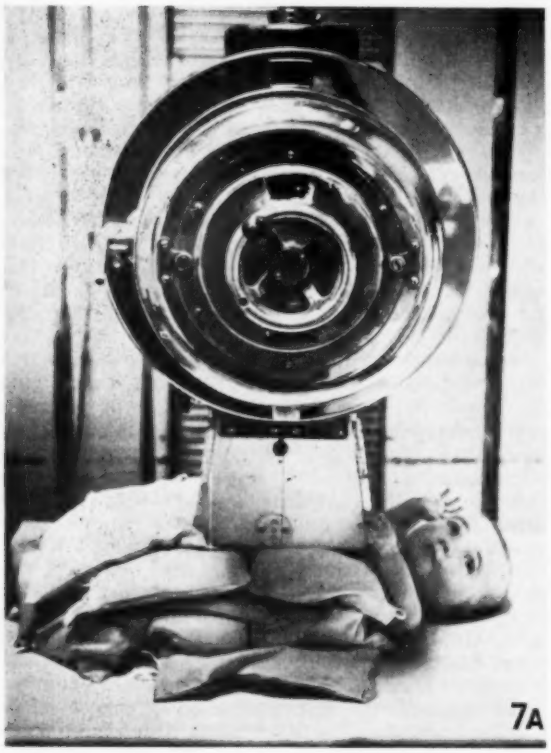
The 3rd large group of tumours includes those occurring in the abdomen. I imagine that the differential diagnosis of a mass in the abdomen of a child presents fewer difficulties in England than it does in South Africa, where there must be many other possible causes of enlarged spleen or liver. The commonest abdominal tumours we encounter are the neuroblastoma and the Wilms' tumour of the kidney. Both are radio-sensitive. Tumours arising in the ovary and testis are not uncommon. The true malignant teratoma of ovary or testis is not radio-sensitive and is only curable if it can be totally removed surgically. On the other hand, the seminoma of the testis and some of the ovarian tumours are sensitive and can be cured by irradiation. I have rarely seen a hepatoblastoma and I have not found this tumour curable by irradiation. In addition, the malignant reticuloses may appear first in the abdomen. Lymphosarcoma and reticulum-cell sarcoma may be successfully treated if they are of limited extent.

I want to discuss briefly the two commonest tumours—the *neuroblastoma* and the *Wilms' tumour*. Their treatment follows almost identical lines but they differ considerably in their clinical characteristics. So let us first look at their clinical features, and then consider for both the method of treatment.

The commonest site of origin of the *neuroblastoma* is in the medulla of the adrenal gland, but it may start anywhere in the sympathetic chain. It is discovered as a mass in the abdomen in a child who has been vaguely unwell or losing weight. The tumour spreads rapidly to lymph-nodes, to the liver, to the lungs and to distant bones, one of the characteristic secondaries being the peri-orbital metastasis which gives the appearance of a bruised eye. A radiograph of the abdomen will not infrequently reveal calcification in the region of the adrenal. The tumour is truly radio-sensitive and if it has not spread beyond the abdomen and chest it can be cured. Unfortunately, many children are first seen when spread has already occurred to the long bones or the head. Cure is not then possible but the child's comfort can be increased by palliative radiation for pain. Recently, it has been suggested that vitamin B12 in large doses is of some value in these cases. We have tried it in incurable cases and I am not satisfied that it had any real effect; it must be remembered that temporary spontaneous regression occurs in about 1 in 10 cases of neuroblastoma.

The Wilms' tumour (nephroblastoma) is truly an embryonic growth. It generally occurs between 1 and 4 years; the oldest case I have seen was in a boy of 11. It is somewhat commoner in girls. The tumour may arise anywhere in the kidney, which it compresses to form a pseudo-capsule. From the kidney it spreads to the aortic nodes, the liver and the lungs. It is unlike the neuroblastoma in that it does not spread quite so quickly and it does not spread to bones. The child has usually failed to gain weight and has a protuberant abdomen with a palpable mass. Intravenous pyelography is an essential part of the investigation. This shows either a failure of excretion on the side of the tumour or else distortion of the kidney pelvis.

The treatment of the Wilms' tumour is a collaborative effort between surgeon and radiotherapist. A combination of irradiation and nephrectomy yields the best curative results. The neuroblastoma is treated by irradiation alone. The technique of irradiation is the same for both types of tumour. The whole abdomen is irradiated from the diaphragm to the pelvis; the upper ends of the femora and the adjacent pelvic bones are excluded as far as possible and it is important to protect for part of the treatment the kidney of the opposite side to the tumour. If this partial protection is neglected, kidney damage may result from the radiation. The abdomen is treated from



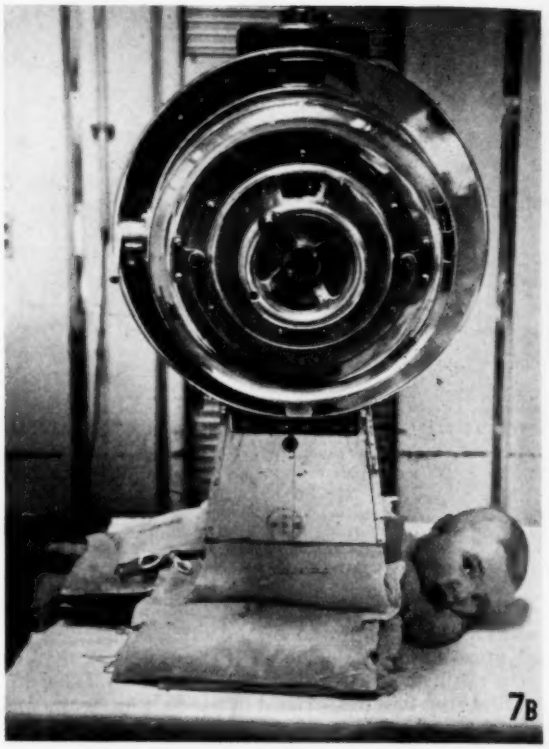


Fig. 7 (*a*). and *Fig.* 7 (*b*). Irradiation of the abdomen in a child of 5 months—(*a*) anterior field, (*b*) posterior field. To illustrate treatment for Wilms' tumour or for neuroblastoma of the adrenal. The size of the treatment field is limited by lead. The contralateral kidney is partially protected with lead.

both front and back on a daily basis for a period of 5 or 6 weeks (Figs. 7 *a* and 7 *b*). The total duration of the treatment varies, depending on the daily dose which is tolerated. We try to achieve a total dose between 2,500 r and 3,000 r. By toleration we mean that the daily input should not cause persistent vomiting nor should it be allowed to reduce the total white-cell count below about 1,800 per c. mm. During treatment the white-cell count remains at a fairly low level and the haemoglobin may fall slightly. Shortly after the end of treatment the blood count begins to improve.

Cases with Wilms' tumour are kept in hospital until the blood count is restored, when nephrectomy is done. This procedure is justified because in the excised kidney it is possible to find tumour cells which appear viable. Sometimes children have already had a nephrectomy when they come for radiotherapy. This is more often the case when the tumour has been relatively small and easy to remove; these children are treated post-operatively in the manner described above. Children are watched very carefully for the first year or so after treatment. This is the period when metastases most commonly occur. If these appear in the liver, nothing further can be done, because the liver has already been treated; if they appear in the lungs, the patient can still be cured by irradiation of the lungs but the cure rate is lower. If we consider those cases of Wilms' tumour in which both irradiation and surgery have been done, the results are good with a 5 year-survival rate of about 40%. The results are slightly better in boys than in girls and they are better in babies under the age of 2 (Tables V and VI).

TABLE V. WILMS' TUMOUR OF THE KIDNEY: 3-YEAR RESULTS ON 41 CASES TREATED 1940-51

	No. Treated	*Survival*
Radical Treatment (irradiation and nephrectomy)	30	40%
Palliative Treatment (irradiation only)	11	0%
	41	29%

TABLE VI. WILMS' TUMOUR OF THE KIDNEY: 5-YEAR RESULTS ON 26 CASES TREATED 1940-49

	No. Treated	*Survival*
Radical Treatment (irradiation and nephrectomy)	19	42%
Palliative Treatment (irradiation only)	7	0%
	26	31%

RETINOBLASTOMA

The last tumour I would like to discuss is also of special interest as being embryonic in type. This is the retinoblastoma. Most of the cases are seen in infants, even in newborns; very few make their first appearance after the 5th year. Most of the cases we see have no family history of the disease. Nevertheless, if a child with retinoblastoma grows up and becomes a parent, the offspring have a very high chance of developing the disease.

The tumour originates in the retina and spreads forwards into the eye, and backwards along the optic nerve to disseminate in the brain. In the advanced case there is also sub-periosteal invasion of the orbital bones and invasion of the neighbouring lymph nodes and soft tissue. In about one-quarter of the patients, the disease is bilateral. These patients with bilateral disease are our greatest challenge.

When the condition is limited to one side, the usual treatment is to remove the offending eye. This is sound treatment, especially if there is no sight in the eye.

Radiotherapy has a real place in curative treatment under certain conditions:

1. If the tumour recurs in the orbit after surgery.
2. If tumour cells are demonstrated histologically in the cut end of the optic nerve after the operation.
3. When the tumour is bilateral. In this situation radiotherapy may then offer the possibility of curing the tumour and of saving at least some sight.

When the eye has already been removed and radiotherapy is necessary to treat a recurrence, X-rays can be applied to the orbit, or radium or radon may be inserted into the orbit. It is important that the dose is sufficiently high to cure this tumour, which is not very sensitive, and it is important that the optic nerve beyond the foramen is included in the high-dose field.

When a baby is brought with a bilateral tumour, there are two problems. The first is to save the child's life and the second is to try to conserve some eyesight. One must decide whether to treat both eyes with radiation or to enucleate the worst eye and to irradiate the other. Radiation is carried out by an implantation of curved needles loaded only at the tips with radon. The group of needle tips is placed to surround the tumour in the plane of the retina.

The radiograph of the implant shown in Fig. 8 was done on a baby boy of 5 months. He came with bilateral disease and the worst eye was enucleated. The better eye had some vision, although even so that tumour was situated on the macula. The ring shown was placed there to measure the magnification so that the position of the needles and the dose could be checked after the implant. This baby is now an 8-year-old schoolboy and although he has a scar in his macula, he is at ordinary school and his teacher reports that he has no apparent trouble with his eyesight.

We have developed in the last few years another method for attempting to conserve vision. This is by making a hollow ring of gold wide enough to surround the tumour. This ring is loaded with radon. The eye is reflected to the side by the ophthalmologist and the ring is then stitched to the sclera to surround the tumour from behind the eye.

Fig. 8. Retinoblastoma. Treatment by implantation of curved needles loaded at the tips with radon.

Alternatively the ring may be shaped like a horseshoe to accommodate the optic nerve. It is too early yet to say whether the ring treatment is an improvement on the insertion of curved needles. With either method it is possible sometimes to conserve some sight. There will always be a scar in the retina where the tumour previously lay, but we have some children who see remarkably well.

The survival of children with retinoblastoma treated by irradiation is shown in Table VII. The prognosis for survival is good and it must be remembered that these cases are not the simple ones. They have come for radiotherapy because there was histological evidence of spread or recurrence after enucleation, or the condition was bilateral. Where an attempt has been made to conserve vision the ability to see has varied. Some are blind, some have useful partial vision, a few see very well. The tumour occurs with equal frequency in boys and in girls, and their chances of survival after treatment are equally good.

TABLE VII. CHILDREN'S TUMOURS: RETINAL GLIOMA: 5-YEAR RESULTS ON 28 CASES TREATED BY RADIATION 1932–49

Sex	*Number Treated*	*5-Year Survival*
Males	15	60%
Females	13	54%
Total	28	57%

THE OVER-ALL PICTURE

The over-all results of treatment of malignant disease of all types in children is shown in Table VIII. You will see that 37% survive at 3 years and 35% at 5 years. Speaking generally, if the child is alive 3 years after treatment, it is likely that he will survive. I think it may be of interest to recall the survival figures for three of the tumours I have discussed. The retinoblastoma shows an equal incidence in boys and girls and the chances of

successful treatment do not depend on the sex. In the Wilms' tumour there are fewer boys than girls and in the boys the prognosis is better; in the medulloblastoma there are fewer girls and their prognosis is the better. The numbers are small but they suggest that the sex which has the least susceptibility to a particular tumour shows the better survival after treatment. This trend has already been shown for some adult tumours by Marion Russell at the Christie Hospital. This finding may point to a principle of wide importance in the biology of malignant disease.

TABLE VIII. CHILDREN'S TUMOURS: ALL SITES: 3-YEAR AND 5-YEAR RESULTS OF TREATED CASES 1932-51

Treated	Survival Rate	Survival Period
436	37%	3-year
351	35%	5-year

There are unfortunately many children with malignant disease for whom cure is impossible with our present methods. What should be the policy in these cases? If the child cannot be cured either because the tumour belongs to an incurable group, for example the sarcoma botryoides, or because it is too extensive, then palliative treatment must be considered. It should only be given even then if it is fairly certain to relieve symptoms to a worth-while extent. I should give as examples of this the treatment of painful orbital metastases of a neuroblastoma, or the equally distressing symptoms of an extensive sacrococcygeal chordoma. In these circumstances treatment should be short and simple so that the child does not spend weary days in hospital undergoing an elaborate and futile treatment. The late Lord Horder put this point of view in a nutshell when he said, 'It is the duty of a doctor to prolong life. It is not his duty to prolong the act of dying.'

In the leukaemias, the commonest of all malignant diseases of children, I used to feel that hospitalization was a mistake and transfusions only raised the parents' hopes for nothing. I now feel strongly that these little patients should be treated with the means at our disposal, and these are increasing. This is the only way that we may, in the end, reach a positive curative technique. But for these children, too, the shorter the time they spend away from their parents the better.

On the other hand, when cure is a possibility then all the resources we have should be brought into play, and no treatment is too meticulous. This is essential, not only that we may cure malignant disease, but also that we do the least possible damage to growing tissues. Many of these patients are going to be well; they will be going to school and must be able to compete in the world with their fellows.

MEETING OF SECRETARIES OF NATIONAL MEDICAL ASSOCIATIONS*

A. H. TONKIN, M.B., CH.B.

Secretary, Medical Association of South Africa

The first meeting of Secretaries of National Medical Associations convened at the World Medical Association (WMA) Secretariat in New York was held on 27 and 28 June 1955. Dr. Austin Smith, Editor of the *American Medical Journal* and Chairman of the United States Supporting Committee of WMA, presided. At the commencement of the meeting the Secretaries were taken on a tour of the offices, and the working of WMA was explained to them. The offices are situated in the Carnegie Building almost opposite the United Nations Building.

After the inspection tour Dr. Louis H. Bauer, Secretary General of WMA, opened the discussion by reviewing the organization and financing of WMA. He stated that WMA was composed of 50 national medical associations, each most representative of the medical profession in the country. The governing body is the General Assembly, which is composed of officers, Council, delegates, alternate delegates, observers and past presidents. Each member-Association is entitled to 2 delegates, 2 alternate delegates and any number of observers. Additional observers represent other national and international bodies interested in medical health problems, such as the World Health Organization (WHO), International Dental Federation, etc. The executive body is the Council, which is composed of the President, President-Elect, Treasurer and 11 Council members, each elected for 3 years. Seven Council members are elected on a regional basis. Sitting with the Council are the Editor, Liaison Officers, Secretary General, Assistant to the Chairman, Executive Assistant and Committee members not members of Council. The Council has Committees as follows: Medical Education, Planning and Finance, Medical Ethics, Miscellaneous Business, International Liaison, and Social Security.

As regards finance, Dr. Bauer stated that at present each member-Association pays dues at the rate of 40 Swiss centimes per member, with a maximum of 20,000 Swiss francs. The Council has authority to adjust its dues in cases of hardship. The Council will recommend to the Ninth General Assembly that the dues be gradually increased as follows: 1956–60 Swiss centimes per member; 1957–80 Swiss centimes per member; 1958–1 Swiss franc per member; and that the ceiling on dues be abolished. Each Association will have the option of paying part of its dues from funds raised outside of its own treasury through a Supporting Committee or through any other means available to the Association. Eventually it is estimated that the treasury would receive 150,000 dollars annually from this schedule, which would be sufficient to finance all activities with the exception of special projects. The expenses of the Association are as follows:

Honoraria and office expenses of Treasurer and Regional Secretaries.

Salary and office expenses of Liaison Officer at Geneva.

Travel expenses of Council members (formerly borne by the United States Committee). This averages about $30,000 annually.

Cost of Council meetings and General Assemblies, including costs of simultaneous translation. The host Association contributes $1,000 to these costs.

Travel expenses of observers sent to other meetings by WMA.

Entire cost of general headquarters and secretariat is now entirely financed by the United States Supporting Committee.

The cost of the publication of the *World Medical Journal* is entirely borne by the United States Supporting Committee at present.

In addition there are printing costs. For example, the Constitution and By-Laws and the Standing Orders are now being reprinted,

* Published by resolution of Federal Council of Medical Association of South Africa.

and Reports of Studies are printed from time to time. Special funds will be required at certain times for special projects such as the Occupational Health Committee, the Medical Education Conference, the Central Repository for Medical Credentials, Meetings relative to International Medical Law, Meetings relative to an international Medical Emblem, and Training Teams for Under-developed Countries.

Dr. Austin Smith stressed the fact that the World Medical Association is frequently confused with the World Health Organization. The latter is an agency of the United Nations and represents the interests of Governments in health and medicine, and is supported through taxation. WMA is the only organization at the international level that can speak for the practising physician. It is non-Governmental and supported by free enterprise. WMA has close liaison with WHO through its Geneva office and by having an exchange of observers at meetings. For example, Dr. Harry Gear, ex-Deputy Chief Health Officer at Cape Town and now Assistant Director-General of WHO in Geneva, is to be the WHO observer at the Ninth General Assembly of WMA in Vienna.

Dr. Macrae of the British Medical Association suggested the need for economies, and Dr. Smith replied that the Planning and Finance Committee of the Council had given intensive study to the possible economies that could be effected. Many of these were being put into practice. It was pointed out that whereas the United States Supporting Committee had previously met all the expenses in connection with Council meetings, it could no longer do so and felt that these expenses should be met by the Organization as a whole. As the United States Supporting Committee at present bears the whole expense of the office in New York and the publication of the *World Medical Journal*, it was felt that this contention was reasonable.

The conference went on to discuss the numerous questionnaires which are sent out by the WMA office to national medical associations. It was pointed out that a considerable amount of useful information was obtained by means of these questionnaires, which was made available to national medical associations and such other organizations as needed to be kept informed authoritatively. The cost of the questionnaires was increased in that they were normally prepared in the 3 official languages of WMA.

International Medical Law. Dr. Bauer stated that the United Nations had raised the question of establishing an International Medical Law for the member countries. This had first been raised some years ago and had been referred to WHO, which had investigated the status of International Medical Law on a factual basis. Now, however, the United Nations had indicated that it considered the subject too broad for WHO and that it should be discussed in its Interagency Council. WMA is unalterably opposed to this, as the Interagency Council of the United Nations is not competent to deal with it. This Council consists of agencies such as ILO, ECOSOC, UNESCO and WHO, all of which are lay agencies except WHO, which is wholly Governmental. It was explained that this whole matter had arisen through a series of mistakes, in that the matter was first raised at a meeting of the Committee on Military Medicine and Pharmacy. As a result of bad translation from the French, the word 'ethics' was translated into English as 'law'. Later on it was intended that the matter should be referred to WMA but it was wrongly referred to WHO and so reached United Nations. Now WMA is faced with the task of seeing that the United Nations give up their project and are satisfied with the International Code of Medical Ethics which WMA has already put out and which has been accepted generally by national medical Associations.

Medical Emblem. Dr. Bauer reported that WMA is interested in establishing an emblem for the use of civilian doctors and civilian defence units that do not qualify under Red Cross Conventions; that this problem had been under consideration for a year and WMA had established that the use of the Red Cross for this purpose could not be extended as it would require another Red Cross Convention and the 1949 Convention had not yet been ratified by a number of countries. The matter was still being pursued.

Central Repository for Medical Credentials. This question had arisen from the fact that at the end of the last war a large number of medical men had found themselves as displaced persons without any proof of their education and medical qualifications due to destruction or loss of records during the war. WMA is investigating the feasibility of its acting as a central repository for certified copies of medical credentials. This, however, would require close cooperation with the secretaries of national medical associations for its implementation. In case of loss of credentials WMA could then supply them on proof of identification. There are numerous complications, including financial ones, but none seems insurmountable. The proposition is being carefully investigated. Apparently the American Medical Association had already devised a 'punch card' record of every doctor in the United States. These records are stored in a rural area for safety in case of bombing, etc.

International Committee on Occupational Health Services. Dr. Bauer reported that WMA has recently appointed an International Committee on Occupational Health Services. Its objective is to raise standards universally and to educate general medical men in the elements of the subject. It also hopes to coordinate the activities of other international organizations in this field, namely WHO, ILO and the International Commission on Industrial Health. Funds are needed to activate the Committee.

Funds for Delegations of National Medical Associations to General Assemblies of WMA. Dr. Bauer stated that the Council had considered the possibility of creating a travelling fund for General Assembly delegates and had suggested that WMA establish a special fund for this purpose based on the pool system used by the British Medical Association in its 'Commonwealth Medical Conference'. This system consists of the pooling of the travelling and subsistence expenses of one delegate from each country. The number of members and the ability to pay is the basis upon which the relative proportion in the sharing of costs is established. In 1954 member-Associations had been circularized relative to this proposal, but so far little favourable comment had been received, and, indeed, most countries in Europe had opposed the idea.

Special Projects. Dr. Bauer stated that the Council had also considered the question of a special fund to finance special projects but stated that it was felt that at times a project for survey or research could well or even best be performed by a national medical association and could perhaps be a subject in which several member-Associations would be qualified to make the necessary study. When such is the situation WMA bespeaks the assistance of the member-Association or Associations in solving the problem presented. To illustrate this, he cited the establishment of a Social Security Research Centre in Stockholm by the Swedish Medical Association and the sponsorship of the Secretariat of WMA by the United States Supporting Committee.

In discussing the future programme of WMA, Dr. Macrae said that he believed that the most valuable service rendered to the British Medical Association by WMA was through its liaison and contacts in Geneva with the numerous international organizations having headquarters there. Dr. George Lull, Secretary of the American Medical Association, agreed with Dr. Macrae that the information and liaison service WMA rendered the American Medical Association on activities of such organizations as the ILO, ISSA etc. was of the utmost value. This activity had helped to make the doctors of the United States conscious of the dangers of Government control. In addition WMA had helped to foster better relations between the national medical associations, and this was bound to be passed down to the individual members of those national associations. Dr. Austin Smith reminded the Secretaries that in Geneva there were some 200 organizational secretariats that had some interest or programmes affecting medicine. Dr. Macrae reported that as a result of the British Medical Association membership of WMA it had adopted a policy of extending invitations to the other member-Associations to send observers to all its General Meetings. Other member-Associations have adopted similar policies. This offers an opportunity for personal contacts between the doctors of the various countries and helps to promote mutual understanding at the individual level.

Supporting Committees. Dr. Bauer reviewed the work of the United States Supporting Committee, which was made up of corporations and individuals. The corporate members may be classified as medical organizations, pharmaceutical firms and other industries. These pharmaceutical and industrial members pay dues in accordance with their business volume as based on a schedule made up by the industrial members of the Board of Directors of the United States Committee. Individual memberships may be of the ordinary, annual or founder group and include

provision for life membership. He suggested that other national medical associations might wish to organize supporting committees in order to assist the payment of their own national dues to WMA.

World Medical Journal. Dr. Bauer reported that the *World Medical Journal* mailing list is revised annually with the assistance of member-Association secretaries. There are now approximately 14,000 doctors located in all areas of the world receiving it. It was hoped that in time there would be at least 100,000 doctors who would read the *World Medical Journal*. Various suggestions were made in order to increase its popularity and Dr. Austin Smith, the Editor of the *World Medical Journal*, said that he would take note of the suggestions.

International Code of Medical Ethics. It was stated tnat a suggestion had been made that the International Code of Medical Ethics should be altered. Various opinions were expressed against this suggestion.

Scientific Meetings. A suggestion was made that there should be scientific meetings held at the same time as the General Assembly of WMA. This matter will probably receive the attention of the Council in due course.

Future Conferences of Secretaries. An attempt was made to evaluate the usefulness of the Secretaries' Conference and possible usefulness of holding similar conferences in the future either at the Secretariat or in connection with the meetings of the General Assembly. The general consensus of opinion was that the first conference had been needed and had served a good and useful purpose; that future meetings should be considered on an *ad hoc* basis; that Secretaries had been able to concentrate their attention on problems of WMA and as a result would give the Association more understanding and cooperation in the future; that the Secretariat should be the venue of these meetings in connection with other meetings in the western hemisphere whenever practicable, and that the Secretary General should not be burdened with any additional meetings at the time of the Annual General Assembly.

Unanimous votes of appreciation were extended to Dr. Austin Smith, who had presided, to the Board of Trustees of the American Medical Association for its hospitality, and to the Board of Directors of the United States Committee. The Secretary General and the staff of the Secretariat were thanked for their cooperation and assistance.

CONCLUSION

In conclusion I would state that in my opinion this meeting of Secretaries of National Medical Associations served an extremely useful purpose. It has given me a knowledge and understanding of WMA which I had not got before, and I feel that this can only be to the good of our Association as a member of WMA. I would like to suggest that Dr. T. C. Routley, at present the President of the British Medical Association and the Canadian Medical Association, who is Consultant-General to WMA and was for a number of years the Chairman of Council of WMA, should be invited to visit South Africa perhaps early next year. Dr. Routley is an outstanding personality in world medical affairs and while Secretary of the Canadian Medical Association the Canadian Government appointed him to be its official representative on WHO. A tour of the country and the Branches of the Medical Association of South Africa by Dr. Routley would do a great deal to stimulate an interest in Association affairs and would bring our members into contact with a man whom it is an inspiration to know.

9TH GENERAL ASSEMBLY OF THE WORLD MEDICAL ASSOCIATION, VIENNA, 1955

A. I. GOLDBERG, F.R.C.O.G.
Cape Town

It was my privilege to attend the 9th General Assembly of the World Medical Association, which was held at the Neues Rathaus, Vienna, on 20-26 September 1955, and for that honour I wish to express my appreciation to the Federal Council of the Medical Association of South Africa.

No more delightful venue for the meeting could have been chosen—Vienna is one of the most beautiful cities in Europe, with a cultural background unsurpassed anywhere. It therefore provided the right atmosphere for debates and discussions of the highest order. Similarly the lighter side of the Congress—the social functions and entertainments for the large number of delegates and observers—was on a lavish scale, and left nothing to be desired.

The Assembly was under the distinguished patronage of the Federal President of Austria, H.E. Dr. T. Körner.

Professor A. Spinelli, President of the WMA, welcomed the delegates and participants. He was followed by Dr. K. Niederberger, President of the Austrian Medical Association, who welcomed the delegates on behalf of the President of Austria, and also on behalf of the Austrian Medical Association. Various other speakers followed, and then the Lord Mayor of Vienna formally declared the 9th General Assembly officially opened.

Dr. K. Niederberger was nominated and unanimously elected President of the World Medical Association for the year 1955-56. Dr. K. A. Holst of the Netherlands was elected the presiding officer for the business sessions of the Assembly.

Although the agenda for the Meeting was a lengthy one, it was so skilfully conducted that all the business was completed on time. It is manifestly impossible to give a résumé of the discussions. The annual report of the Council was submitted, and the reports of the Regional Secretaries representing Asia, Australia, Europe and the Latin Americas. Then there were very interesting and comprehensive reports by Council Committees—on Medical Education by Sir Lionel Whitby, and on Medical Ethics by Dr. Cibrie of France—also reports by the WMA observers appointed to other International organizations. Thus Dr. Jean Maystre, the Official Liaison Officer, reported on the World Health Organisation, the International Labour Organization, and the International Security Association. Dr. Cibrie reported on UNESCO and CIOMS. Dr. Gloneux of Belgium reported on the International Congress of Military Medicine and Pharmacy.

The WHO report, for example, dealt with the problems of atomic energy in relation to medicine; viz. (1) Problems of health protection against radiation, and (2) medical use of radio-isotopes.

Front, from left to right: Dr. A. I. Goldberg, Dr. Mallen (Australia), an Austrian delegate.

It was felt that the conscience and wisdom of mankind should be directed to the peaceful, as against the destructive, application of atomic energy.

TWELVE PRINCIPLES OF MEDICAL PRACTICE IN SOCIAL SECURITY

A good deal of time was given to the report drawn up by Dr. Dag Knutson on 'Social Security in the Field of Health Care'. The increasing cost of Medical Services—administration, medicaments, hospitalization, and social-security cash-benefits—was stressed, and one heard a good deal of the 'Twelve Principles of Social Security' adopted by the WMA, and as these are probably not known to many members of our Association, they might be well worth quoting *in extenso*.

'Whenever medical care is provided as part of Social Security, the following principles should govern its provision:

1. Freedom of choice of physician by the patient. Liberty of physician to choose patient except in cases of urgency or humanitarianism.

2. No intervention of third party between physician and patient.

3. Where medical service is to be submitted to control, this control should be exercised by physicians.

4. Freedom of choice of hospital by patient.

5. Freedom of the physician to choose the location and type of his practice.

6. No restriction of medication or mode of treatment by physician, except in cases of abuse.

7. Appropriate representation of medical profession in every official body dealing with medical care.

8. It is not in the public interest that physicians should be full-time salaried servants of the government or social-security bodies.

9. Remuneration of medical services ought not to depend directly on the financial condition of the insurance organization.

10. Any social security or insurance plan must be open to the participation of any licensed physician, and no physician should be compelled to participate if he does not wish to do so.

11. Compulsory health insurance plans should cover only those persons who are unable to make their own arrangements for medical care.

12. There shall be no exploitation of the physician, the physician's services, or the public, by any person or organization.'

I have already mentioned that the social functions and entertainment of the delegates left nothing to be desired; everything was on a lavish scale. There was a most enjoyable reception by the Lord Mayor. The gala concert by the Vienna Philharmonic Orchestra in the Grössen Musik Vereinsaal attracted a very large and appreciative audience. The Federal Minister of Social Administration gave a delightful party. There was an outstanding gala performance at the opera, and this is something at which the Viennese excel. There were also excursions through Vienna and its delightful surroundings, a convivial evening at Grenzing, and a formal annual dinner given by the Austrian Medical Board. A medical, technical and pharmaceutical exhibition was well organized, as well as an exhibition of medical documents, historical medical instruments, and the famous wax collection of anatomical models.

From left to right: Dr. A. I. Goldberg, Dr. H. S. Gear (Assistant Director General, WHO), Mrs. Gear.

I came away from the meeting with the feeling that many of our members were hardly aware of the existence, let alone the functions and achievements of the World Medical Association. I was greatly impressed by the type of individuals who form the Council and direct its activities—these gentlemen who give up so much of their time, energy and leisure in furtherance of the advancement of the medical profession the world over.

OBJECTS AND ACCOMPLISHMENTS OF WMA

Perhaps it would serve a useful purpose if I summarized what Dr. Louis M. Bauer, the Secretary General, wrote:

'The World Medical Association has become a world-wide organization, recognized not only by doctors, but by the Governments and International organizations, and it is now beginning its 9th year of service.

'The WMA is an organization of National Medical Associations. At present some 52 Associations are members.

'There is a growing need today for honesty, mutual trust and understanding, not just on the individual and national levels, but especially on the international level.

'The doctors comprising the World Medical Association have been far-seeing enough to recognize that medicine offers a basis of mutual understanding, respect and cooperation. They have demonstrated that it is possible to further the advance of medical science, and to obtain the humanitarian objectives of the medical profession, through collaboration in a world organization without surrendering any of their national prerogatives or violating any of their national traditions.

'The most important aims are to effect a better liaison among the doctors of the world; to afford a forum for discussion of world medical problems; to distribute information; to raise the standards of medicine, medical education and health; to speak for the practising profession before other international bodies; and to improve international relations.

'The Association is governed by a General Assembly, which is composed of 2 delegates from each member association, 2 alternate delegates, observers from national and international bodies, together with the officers and Council. The Assembly meets annually. Thus each member association, regardless of its size, has the same voting strength.

'The Association is not primarily a scientific organization, but is interested in scientific problems. A scientific session is held each year in connection with the General Assembly. There is also a session devoted to medical journalism.

'Perhaps the outstanding accomplishment of the WMA was the sponsoring of the 1st World Conference on Medical Education in 1953—there were in attendance over 600 delegates from 62 countries, and representing 127 medical schools and universities. A 2nd World Conference is planned for 1959 to be held in the USA.

'Also among the accomplishments of the Association are the modernization of the Hippocratic Oath, known as the Declaration of Geneva, and the adoption of the International Code of Medical Ethics; surveys of medical education, both undergraduate and postgraduate; continuing studies on social security as it affects the practice of medicine, together with the adoption of the 12 principles on the same subject.

'Thus the Association in the past 8 years has been responsible for developing more mutual trust and understanding among individuals of the world than have the government diplomatic services. It has aided in the promotion of international goodwill, and has proved beyond any reasonable doubt that, although the 700,000 doctors of the Association speak many different languages, the language of medicine is universal.'

NATIONAL GENERAL PRACTITIONERS' GROUP

The Annual General Meeting of the National General Practitioners' Group was held at Pretoria University on 19 October 1955 at 2.30 p.m.

Dr. J. J. van Niekerk took the chair and 29 members were present. Tributes were paid to Drs. E. Meltzer and M. Shapiro for what they had done during the year.

Secretary's Report

The Steering Committee had been elected in 1952 and, as a fully constituted National Committee had not been formed, had been appointed to remain in office. The Committee had met frequently and Dr. M. Shapiro had acted as chairman during Dr. J. J. van Niekerk's absence through ill-health.

The membership of the Group was 668, by branches as follows: Southern Transvaal 217, Cape Western 111, Natal Coastal 99, Border 58, East Rand 46, Cape Midlands 43, Northern Transvaal 36, Griqualand West 21, OFS 16, Natal Inland 11, Transkei 8, others 2.

Specialist Register. Reference was made to the even voting in the Medical Council on this matter. 'It is up to the G.P. Group to take the necessary steps to have the Amended Act withdrawn and the Specialist register replaced by a Consultant register.'

College of Physicians and Surgeons. Members attended the inaugural meeting and held a watching brief for the Group. It is hoped that the College will cater for all sections of the profession without discrimination and will further all forms of postgraduate opportunity and education, particularly for GPs. We have resisted the formation of a GP section of the College, and recommend GPs to join as Founder Members.

Section 80bis of Medical, Dental and Pharmacy Act. This Section has proved in practice to operate better than the old Section 80.

Medical Practice. The efforts of the Group have stimulated the establishment of a course for GPs at Pretoria University, and the meetings of the Witwatersrand Medical Graduates Association have been thrown open to the whole profession.

Medical Aid Societies. Federal Council has instituted a committee to inquire into the desirability of establishing Medical Aid fees on a geographical basis. At present they are uniform throughout the country, which in the view of this Group is unrealistic.

Groups of the Association. The Steering Committee has forwarded a resolution to Federal Council asking for the abolition of Groups within the Association.

General practitioners have become more conscious of their strength and stature in the profession, and must work for equality with specialists in the eyes of the law and the profession. They require further postgraduate opportunities and posts on hospital staffs. The Group should not be used for the purpose of obtaining higher fees.

The Secretary's report was adopted.

The Financial Report and Balance Sheet were adopted unanimously, and auditors were appointed.

A full report was presented by members of Steering Committee who had been present at the meeting of Federal Council held in October 1955.

On the question of the Specialist register it was decided to await the results of the new committee set up by Medical Council to deal with the subject. Dr. C. Shapiro, a member of that committee, said he would welcome memoranda from GPs on the subject.

Workmen's Compensation Act. A long discussion ensued on the difficulties under this Act.

MEDICAL DEGREES CONFERRED AT THE UNIVERSITY OF CAPE TOWN

The following medical degrees were conferred at the University of Cape Town after the examinations in November 1955:

M.D.

E. J. Salber, M.B., Ch.B., D.P.H.
T. L. Sarkin, M.B., Ch.B., Ch.M.

Ch.M.

B. J. v. R. Dreyer, M.B., Ch.B., M.D.

M.Med. (Anaesthetics)

L. Atkins, M.B., Ch.B.
P. H. B. Maytom, M.B., Ch.B.
L. S. Meyerovitz, M.B., Ch.B.

M.Med. (Pathology)

T. G. Sacks, M.B., Ch.B.

Final Year M.B., Ch.B.

G. G. Archer
N. L. Becker
I. R. Berelowitz
J. M. Blomerus
J. N. Booysen
T. P. Boulle
I. Brajtman
A. C. K. Brink
Miss S. Brink
J. W. Bruwer
Miss S. C. H. Chait
Miss D. M. Chisholm
C. W. F. Clarke
G. C. M. Clarke
J. A. Collie
R. S. Damonze
A. B. Daneel
Miss A. M. Dollery
J. L. du Plessis
J. N. du Toit
R. W. Duursma
M. Elstein
H. R. Esser
A. G. W. Farrell
W. M. P. Fennell
Miss R. M. Fisher
J. L. Goldberg
H. T. Goodman
Miss S. C. F. Greyling
J. B. Gurland
Miss D. Haberer
B. W. Hellberg
H. L. Hoe Easton
S. H. Ismail
Miss W. J. Israelsohn
H. G. Jardine
S. Jhinku
E. L. Judkowski
M. Kaplan
J. B. Labia
I. Lemonsky
P. A. J. le Roux
L. E. Levenson
J. Levit
S. Lewitton
B. Lind
H. Maisel
M. B. McKenzie
A. M. Michalowsky
E. E. D. Mills
J. P. Möller
J. E. Nel
J. P. Nel
L. H. Opie
B. L. Pimstone
F. P. Retief
W. M. Rigal
C. R. Robertson
I. Sakinofsky
A. C. Schaffer
J. H. B. Smith
I. Spector
A. H. Stegen
J. C. Strauss
Miss J. M. Talbot
G. N. Thatcher
S. T. Trezise
H. W. Truter
J. J. van der Walt
P. A. van Jaarsveld
D. J. J. van Velden
B. J. Verster
M. von Thomann
H. J. Voortman
C. E. Watson
T. F. Weich
P. Wisnowitz
W. Wittmann
B. J. Wolff

PASSING EVENTS : IN DIE VERBYGAAN

The 1st International Congress of Human Genetics will be held in Copenhagen, Denmark, on 1-6 August 1956. The Danish honorary committee and organizing committee are assisted by national committees or representatives in many of the principal countries of the world. The Congress is planned to cover all genetic aspects of normal and pathological characters in man. Any person interested in the subject of human genetics and especially of medical genetics is invited to take part in the Congress. The provisional programme and other information will be sent on request being made to the Congress Secretariat, University Institute for Human Genetics, 14 Tagensvej, Copenhagen N, Denmark. The Congress programmes will be in English only. The official languages will be English, French and German, but English is recommended for the presentation of papers. The Congress fee

up to 1 April 1956 is 150 Danish kroner, but after that date 225 Danish kroner. Families and friends of members may be enrolled as associates for a fee of 50 Danish kroner before 1 April 1956, and 100 Danish kroner thereafter. Only Danish kroner will be accepted. On cancellation before 1 July 1956 fees will be refunded less 20%, but not later. The hotel situation in Copenhagen is difficult, and those who want the Congress office to assist them in procuring accommodation should request this not later than 1 February 1956.

* * *

The Society for the Study of Fertility, London. The Society's next Annual Conference will be held on 14 and 15 June 1956—on 14 June at the Meeting House of the Zoological Society of London, and on 15 June at the National Institute for Medical Research, Mill Hill, London. Further information may be obtained from the Secretary, Mr. H. H. Fouracre Barns, F.R.C.S., M.R.C.O.G., 31 Weymouth Street, Portland Place, London, W. 1.

Dr. A. Landau, of Cape Town, has been appointed to be a member of the Executive Committee of Federal Council *vice* Mr. M. Cole Rous deceased. This appointment has been made by the Chairman of Council in accordance with Standing Order 30.

* * *

Union Department of Health Bulletin. Report for the 7 days ended 1 December 1955.

Plague, Smallpox: Nil.

Typhus Fever. Cape Province: Two (2) Native cases in the Glen Grey district. Diagnosis confirmed by laboratory tests.

Epidemic Diseases in Other Countries.

Plague: Nil.

Cholera in Calcutta (India); Dacca (Pakistan).

Smallpox in Kabul, Kandahar (Afghanistan); Rangoon (Burma); Ahmedabad (India); Dacca (Pakistan).

Typhus Fever in Kabul (Afghanistan); Alexandria, Cairo (Egypt).

BOOK REVIEW : BOEKRESENSIE

THE PHARMACOTHERAPY OF FEVER

Pharmakotherapie Des Fiebers und der fieberhaften Affektionen. Deur Drs. R. Isenschmid, E. Glanzmann, H. Berger and T. Gordonoff.

Inhalt: 1. Die Patho-Physiologie des Fiebers. 2. Klinik der fieberhaften Affektionen. 3. Pharmakologie und Toxikologie der Antipyretica. Sachregister.

In the first part of the book, the patho-physiology of fever is discussed. The author gives an exhaustive description of the different types of fever and feverproducing agents. The therapeutic use of fever is discussed. An extensive literature index is given.

The second part of the book deals with the clinical aspect of febrile diseases. As in the first part of this book, the author again describes the normal body temperature, its regulation and alterations. This repetition is not necessary. The pathology and therapy of febrile diseases are dealt with clearly. Fever as a typical sign of disturbed functions of the body is discussed in cases of virus, bacterial or rickettsial infections. At the end of this chapter an extensive list of drugs is given which are related to fever. Nearly all known chemotherapeutics and antibiotics are listed as well. A good literature index is given.

The third chapter deals with the pharmacology and toxicology of antipyretica. This could be done in much more detail. So many pharmacological data are scattered in the previous chapters. The literature index is poor and many pharmacological papers are again quoted in other parts of the book.

Although the subject is not developed methodically, this book can be recommended. It gives to those, who understand German, a profound knowledge of the manifold aspects of fever as an expression of illness, and its therapy. M.W.

CORRESPONDENCE : BRIEWERUBRIEK

RELAXANTS IN ANAESTHESIA

To the Editor: Your editorial *Safety First in Anaesthesia*,[1] in your issue of 19 November 1955, is based mainly on a paper by Beecher and Todd published in July 1954. The gist of this report was conveyed rather alarmingly to the lay public by the American periodical *Time* in July 1954, describing anaesthesia under the heading 'Pain and Patient Killer'.

With masterly understatement you point out that 'it failed to gloss over the startling results of analysis of the use of relaxants'. To my mind no attempt was made to gloss over anything. Beecher and Todd go out of their way to emphasize that in the hands of the anaesthetic services of 10 American university hospitals relaxants are held responsible for far too many deaths. The original paper is long, contradictory, confusing and misleading. As the Editors of the *Lancet* pointed out, on one page alone in two tables side by side are such conflicting figures that it is difficult to understand what the authors really mean.

As every anaesthetist knows, in this country at any rate, the relaxants, by partial or complete paralysis of the respiratory muscles, cause respiratory depression or even arrest. An obvious corollary to this is that respiration must be assisted or controlled as long as there is any depression of spontaneous respiration. Yet Beecher and Todd in Table XXV admit that respiratory failure (hypoxia) was responsible for 63% of the 'curare deaths'. In practice no patient should die from hypoxia due to the use of relaxants or respiratory depressant drugs, so that 63% of the 'curare deaths' were preventable—and yet in Table XXIV 'gross errors in management in curare deaths' are listed as only 10%. The last half of Table XXV contradicts both these figures—here admitted errors in technique account for 79% of 'curare deaths'.

This phrase 'curare deaths', too, I regard as particularly misleading. Beecher and Todd themselves admit that they use it to include all deaths occurring in patients to whom some relaxant has been given, and go on to admit themselves that they do not know that 'curare' has killed a single patient. Such loose nomenclature gives rise to very false belief—in this country we are already saddled with a phrase 'anaesthetic deaths' meaning death occurring whilst under an anaesthetic, but including all deaths due to errors in surgical technique.

Table XXII of Beecher and Todd purports to show death rates with various specified relaxants, but a footnote explains that only those cases are counted where the relaxant was specified. Obviously a note of the specific relaxant used was made in every case when the patient died, but only in well under half the cases when the patient survived—in 16,560 cases out of a possible 44,000—and yet the 'death rate' is tabulated as against the lower figure, an error of some 200-300%!

Beecher and Todd's assumption that 37% of so-called 'curare deaths' are due to 'cardiovascular failure notwithstanding artificial respiration' is merely a pet theory of their own, contrary to generally accepted clinical and pharmacological opinion, and they quote no case records in support of their fanciful hypothesis.

As you point out in your editorial, only 10% of the anaesthetics were given by specialist anaesthetists. More than twice this number in the series were given by nurses, and 'anesthesia residents' and medical students are also listed. You say all the anaesthetics were supervised by specialists. All I can say is that the supervision was totally inadequate.

Another table of Beecher and Todd shows that there is no difference in the type of cases anaesthetized by nurses and specialists. Again all I can say is that there ought to be. The idea of entrusting poor-risk cases to be anaesthetized by technicians using drugs as potent as the relaxants quite frankly appalls me. In this country we are lucky—we have successfully resisted an attempt to take the retrograde step of allowing nurses to give anaesthetics.

Beecher and Todd admit that they 'do not have evidence that the muscle relaxants affect the overall death rate in surgical pa-

tients'. Does this mean that the 'alarming ratio of 1 death in 192 anaesthetics' has been manipulated by now blaming 'curare' for the deaths that have always occurred in surgery? The paucity of the figures quoted by Beecher and Todd shows that, in the institutions concerned, the administrators—I won't say anaesthetists—were only beginning to use these powerful drugs, and the results shown include the teething troubles of successive generations of learners. 44,000 anaesthetics with relaxants in 10 hospitals over 5 years is less than 1,000 relaxant cases a year per hospital. There are many anaesthetists in this country who do more than that themselves, and I can assure you with nothing like that appalling death rate.

Frankly, the fault does not lie in the drugs but in the way they are used or misused. A famous anaesthetist in England during the early days of cyclopropane was asked if he did not think that the cyclopropane was dangerous. He replied, 'Yes, if you don't use it properly; even a bucket of water is dangerous if you stick your head in it'.

Your editorial seems to me unfair in that it presents only one side of the picture, presenting a few data culled at random from Beecher and Todd's paper, and failing to mention any of the very cogent criticisms of their findings that have appeared in the medical press in the past sixteen months.

F. W. Roberts
President
South African Society of Anaesthetists
309 Harley Chambers
Jeppe Street
Johannesburg

2 December 1955

1. Editorial (1955): S. Afr. Med. J., **29**, 1084.

MEDICAL ETHICS AND ADVERTISING

To the Editor: The facts are laconic and nebulous but it would appear that we have recently been treated to the singular phenomenon of a medical practitioner being cautioned for contravening one of the ethical rules, namely, advertising, in that he did write a short story under a nom-de-plume. The story won a first prize, thereby gaining vicarious publicity for the author through the publishing house which might be instrumental in further exploiting him for its benefit. An incident of this nature cannot but bring to mind examples of some renegades from the medical profession who have achieved fame in the field of letters.

It may be that the appointed authorities responsible for maintaining the high standard of medical ethics as well as being the guardians of the Platonic theory of literacy and education amongst members of the profession, mindful of—not *The Citadel* (a competently written novel with an underlying gauche manifestation of sour-grapes)—but *Hatter's Castle*, rightly decided that another such immature effort could reflect but little credit on a doctor-author in particular and on the profession as a whole. Nevertheless it is on record that the late Francis Brett Young, who achieved in literature the Everest of his ambition, had poems published while he was still in active practice, and decided to substitute the pen for the stethoscope some years before publication of *A Portrait of Clare* (which won for him the coveted James Tait Black Memorial Prize) and *My Brother Jonathan*, rated high as one of the best novels portraying the tradition of medical practice.

The late Robert Bridges at one time held the post of medical registrar at Great Ormond Street Hospital for Children and abandoned the practice of medicine in early middle age. It must be assumed that in the one case the publicity attaching to his literary output must have made the name of Francis Brett Young widely known, and in the second case Robert Bridges must have gained high praise with the publication of a long list of poems under his own name before Royalty was sufficiently impressed to appoint him Poet Laureate.

Somerset Maugham in a preface to an edition of *Liza of Lambeth* (his first-born) takes great delight in describing how his publisher, in order to publicize the book, sent copies to various dignitaries of the Church. One thought it sufficiently interesting to make it the subject of a Sunday morning sermon, whilst the other was so nauseated by its contents that he threw the book into the Thames. On the strength of the enormous publicity so adroitly manoeuvred the publisher turned an overdraft into a balance (and in a moment of aberration, no stipulation concerning royalties having been made, gave the author £25) and Maugham, having recently qualified, was offered the post of assistant-accoucheur at St. Thomas' Hospital.

Reason should be interwoven with logic and a doctor who has a talent (more often an urge) for writing should not be disappointed if he is allowed but a thin slice for an effort from which his publisher makes a large profit. The latter, not being versed in the medical code of ethics, considers the publicity gained by the actively practising doctor sufficient reward. In such a case, however, legislation at the highest level should prescribe that erasure of the doctor's name from the medical register on account of this publicity should be *a priori* grounds for the publisher to remunerate him in a manner commensurate with the publicity he would have attained had he been allowed to remain in active practice.

If publicity of such a nature is regarded as crossing the ethical code a doctor in practice whose son had achieved fame in another sphere might find himself impugned for unethical conduct. A figure that at once springs to mind is Oscar Wilde, whose immortal plays and brilliant epigrams must have reflected a halo around his father's ophthalmological practice as great as the unwanted publicity he later had to bear following on the revelations which are now history. Of course laws could be promulgated to ban publication of works by close relatives of practising physicians but it is debatable whether such an act would be in the best interests of culture. It is a question of whether we prefer Oscar Wilde with his brilliance and perversion or would have him normal, dull and unproductive, in which case, *Lady Windermere's Fan*, *The Importance of Being Earnest*, and *The Ballad of Reading Gaol* would be lost to the world.

Another writer who did not altogether conform to a recognized conventional way of life and whose father practised the art of medicine, was Francis Thompson. Alice Meynell informs us that long after Francis had composed and published *The Hound of Heaven*, and *In No Strange Land*, Dr. Thompson, when asked why he had treated his son so shabbily, replied, 'I did not know he could write the stuff'.

Immortal and illustrious names now crowd the excited mind, clamouring for inclusion, but space allows mention of only two: Conan Doyle sitting in his Southsea surgery, gazing apprehensively at an empty waiting-room and subconsciously hoping no patient would enter to disturb his thoughts busily engaged in creating Sherlock Holmes, and O. H. Mavor (James Bridie), who found time to write all his fascinating plays (*The Anatomist*, *Tobias and the Angel*, *Jonah and the Whale*, and *The Sleeping Clergyman*—this last a play about genius and the futility of trying to breed for perfection from human stock) while holding the Professorial Chair of Medicine at Anderson's College, as well as maintaining his position of visiting physician to the Glasgow Victoria Infirmary.

Some years ago Lord Moran at a Harveian dinner stated: 'Whilst medicine has riveted the attention and absorbed the energies of the ablest of our race, the government of man, which is the business of politics, is the greatest of all human studies'. One would like to think that the guardians of medical morals are not less versed in human understanding than are the politicians who govern a country, and, whilst to the laity, inexperienced in medical ethics, it may appear that the bureaucratic mind thoughtlessly maintains the *status quo* with an occasional random example,

('I do not like thee Dr. Fell,
The reason why I cannot tell . . . .')

that body may act not without reason, taking its cue from Othello's last words:

'Nothing extenuate nor set down aught in malice'.

It is fervently to be hoped that the name of Albert Schweitzer will not be erased from the medical register.

Joseph B. Lurie

Klipfontein Organic Products Corporation
Johannesburg

18 November 1955

[The medical practitioner who won the prize with a story written under a nom-de-plume asked the South African Medical Council whether there would be any objection to the publication of his photograph in the press, to his receiving a public reception by the Mayor of Johannesburg, and to his receiving publicity in Paris (all these under his nom-de-plume). The Executive Committee of the Council advised him that this would be contrary to the traditions of the profession and that if a complaint were lodged the Council might have to take cognizance of it. The Council did not caution the doctor for having written a story under a nom-de-plume or for any contravention of ethical rules.—*Editor*]